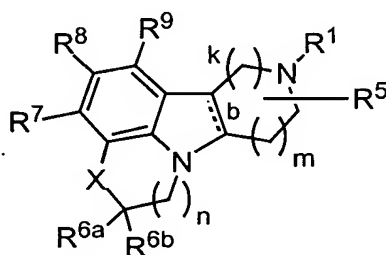


SUBSTITUTED HETEROCYCLE FUSED GAMMA-CARBOLINES**CROSS-REFERENCE TO RELATED APPLICATIONS**

This application is a continuation-in-part of co-pending U.S. Patent
5 Application Serial No. 10/370,872 filed on February 20, 2003 which is a divisional of
U.S. Patent Application Serial No. 09/594,008 filed on June 15, 2000, now U.S.
Patent No. 6,548,493, which claims priority from U.S. Provisional Application No.
60/139,321 filed June 15, 1999.

10 FIELD OF THE INVENTION

The present invention is directed to certain novel compounds represented by
structural Formula (I)

**(I)**

or pharmaceutically acceptable salt forms thereof, wherein R¹, R⁵, R^{6a}, R^{6b}, R⁷, R⁸,
R⁹, X, b, k, m, and n, and the dashed lines are described herein. The invention is also
concerned with pharmaceutical formulations comprising these novel compounds as
20 active ingredients and the use of the novel compounds and their formulations in the
treatment of certain disorders. The compounds of this invention are serotonin
agonists and antagonists and are useful in the control or prevention of central nervous
system disorders including obesity, anxiety, depression, psychosis, schizophrenia,
sleep disorders, sexual disorders, migraine, conditions associated with cephalic pain,
25 social phobias, and gastrointestinal disorders such as dysfunction of the
gastrointestinal tract motility.



23914

PATENT TRADEMARK OFFICE

BACKGROUND OF THE INVENTION

There exists a substantial correlation for the relationship between 5-HT₂ receptor modulation and a variety of diseases and therapies. To date, three subtypes of the 5-HT₂ receptor class have been identified, 5-HT_{2A}, 5-HT_{2B}, and 5-HT_{2C}.

5 Prior to the early 1990's the 5-HT_{2C} and 5-HT_{2A} receptors were referred to as 5-HT_{1C} and 5-HT₂, respectively.

The agonism or antagonism of 5-HT₂ receptors, either selectively or nonselectively, has been associated with the treatment of various central nervous system (CNS) disorders. Ligands possessing affinity for the 5-HT₂ receptors have
10 been shown to have numerous physiological and behavioral effects (Trends in Pharmacological Sciences, 11, 181, 1990). In the recent past the contribution of serotonergic activity to the mode of action of antidepressant drugs has been well documented. Compounds that increase the overall basal tone of serotonin in the CNS have been successfully developed as antidepressants. The serotonin selective
15 reuptake inhibitors (SSRI) function by increasing the amount of serotonin present in the nerve synapse. These breakthrough treatments, however, are not without side effects and suffer from delayed onset of action (Leonard, J. Clin. Psychiatry, 54(suppl), 3, 1993). Due to the mechanism of action of the SSRIs, they effect the activity of a number of serotonin receptor subtypes. This non-specific modulation of
20 the serotonin family of receptors most likely plays a significant role in the side effect profile. In addition, these compounds often have a high affinity for a number of the serotonin receptors as well as a multitude of other monoamine neurotransmitters and nuisance receptors. Removing some of the receptor cross reactivity would allow for the examination and possible development of potent therapeutic ligands with an
25 improved side effect profile.

There is ample evidence to support the role of selective 5-HT₂ receptor ligands in a number of disease therapies. Modulation of 5-HT₂ receptors has been associated with the treatment of schizophrenia and psychoses (Ugedo, L., et.al., Psychopharmacology, 98, 45, 1989). Mood, behavior and hallucinogenesis can be
30 affected by 5-HT₂ receptors in the limbic system and cerebral cortex. 5-HT₂ receptor modulation in the hypothalamus can influence appetite, thermoregulation, sleep, sexual behavior, motor activity, and neuroendocrine function (Hartig, P., et.al.,

Annals New York Academy of Science, 149, 159). There is also evidence indicating that 5-HT₂ receptors mediate hypoactivity, effect feeding in rats, and mediate penile erections (Psychopharmacology, 101, 57, 1990).

Compounds exhibiting selectivity for the 5-HT_{2B} receptor are useful in treating conditions such as tachygastria, hypermotility associated with irritable bowel disorder, constipation, dyspepsia, and other peripherally mediated conditions.

5-HT_{2A} antagonists have been shown to be effective in the treatment of schizophrenia, anxiety, depression, and migraines (Koek, W., Neuroscience and Behavioral reviews, 16, 95, 1996). Aside from the beneficial antipsychotic effects, classical neuroleptic are frequently responsible for eliciting acute extrapyramidal side effects and neuroendocrine disturbances. These compounds generally possess significant dopamine D₂ receptor affinity (as well as other nuisance receptor affinity) which frequently is associated with extra pyramidal symptoms and tardive dyskinesia, thus detracting from their efficacy as front line treatments in schizophrenia and related disorders. Compounds possessing a more favorable selectivity profile would represent a possible improvement for the treatment of CNS disorders.

Serotonin (5HT) may have a critical role in the regulation of some drug-induced addictive behaviors. Serotonin is involved in neuronal processes related to inhibitory control and impulsivity. (Roy et al., Acta Psychiatr. Scand. 78 (1988) 529-535; Soubrie et al., Behav. Brain. Sci. 9 (1986) 319-364) Some studies have implicated serotonergic mechanisms in the development or expression of drug-induced sensitization (King et al., Psychopharmacology 130 (1997) 159-165; Olausson et al., Psychopharmacology 142 (1999) 111-119) The relationship between 5HT and impulsive behavior as well as drug intake has been described, and manipulations that attenuate 5HT neurotransmission both increase impulsive behavior (Roy et al., Acta Psychiatr. Scand. 78 (1988) 529-535; Soubrie et al., Behav. Brain. Sci. 9 (1986) 319-364) and elevate the intake of various drugs of abuse (Engel et al., in Naranjo, C.A., Sellers, E.M. (Eds.). Novel Pharmacological Interventions for Alcoholism, Springer, New York, pp. 68-82 (1999); Roberts et al., Pharmacol. Biochem. Behav. 49 (1994) 177-182)

A series of animal investigations have reported that central 5HT₂ receptors are related to the many symptoms associated with drug-dependent withdrawal.

Withdrawal from chronic exposure to low doses of cocaine causes reversible supersensitivity of 5HT₂ receptors in mice. (Baumann et al., *Neuropharmacology* 35 (1996) 295-301; Darmani et al., *Neurotoxicol. Tertol.* 22 (2000) 61-69) Moreover, the 5HT₂ receptor antagonists, ketanserin and mianserin, block or attenuate morphine withdrawal syndrome in rats. (Neal et al., *J. Pharmacol. Exp. Ther.* 236 (1986) 157-165; Neal et al., *Eur. J. Pharmacol.* 132 (1986) 299-304)

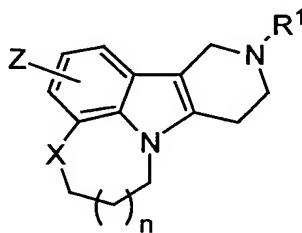
The effects of 5HT receptor agonists on the behavioral and neurochemical consequences of repeated nicotine treatment have also been studied. (Olausson et al., *Eur. J. Pharmacol.* 420 (2001) 45-54) The results of that study provided evidence that repeated daily nicotine treatment is associated with both locomotor sensitization and behavioral disinhibition, and that the expression of those behaviors can be modulated by specific agonists at 5HT receptor subtypes.

Studies with experimental animals have shown that nicotine withdrawal leads to increased sensitivity of serotonergic neurons in the dorsal raphe to 5HT_{1A} agonists in rats. (Rasmussen et al., *Psychopharmacology (Berl)* 133 (1997) 343-346) Other findings suggest that cessation of chronic nicotine increases the sensitivity to 5HT₂ receptor systems, and that the 5HT₂ receptor systems may be related to some aspect of the nicotine withdrawal syndrome. (Suemaru et al., *Psychopharmacology (Berl)* 159 (2001) 31-38) Other studies have also examined the effect of nicotine cessation on the central serotonergic systems in mice and the involvement of 5HT₂ receptors. (Yasuda et al., *Naunyn-Schmiedeberg's Arch. Pharmacol.* 366 (2002) 276-281) The studies by Yasuda et al. suggested that cessation of repeated nicotine administration resulted in increased sensitivity to 5HT₂ receptor systems and decreased 5HT₂ turnover, and that these phenomena may be related to the manifestation of nicotine withdrawal symptoms.

Modulation of the 5-HT₂ receptors has been observed to play a role in sleep disorders. Ritalanserin, a selective 5HT₂ receptor antagonist, massively enhances slow wave sleep (stage 3 and 4) in humans (Declercq et al., *Curr. Ther. Res.* 41 (1987) 427-432; Idzikowsky et al., *Psychopharmacology* 93 (1987) 416-420; Idzikowsky et al., *Brain Res.* 378 (1986) 164-168) and increases deep slow wave sleep in rats. (Detari et al., *Psychopharmacology* 142 (1999) 318-326; Dugovic et al., *Eur. J. Pharmacol.* 137 (1987) 145-146; Kantor et al., *J. Physiol.* 526 (2000) 66-67) Ritalanserin and other

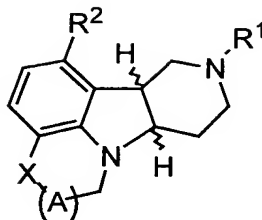
5HT2 receptor antagonists increase low frequency EEG activity administered at the beginning of the passive phase of sleep, that is in the light period in rats (Borbely et al., Eur. J. Pharmacol. 156 (1988) 275-278) and in the dark period in humans (Dijk et al., Eur. J. Pharmacol. 171 (1989) 207-218).

- 5 The effects of the 5HT2 receptor antagonist ritanserin on electroencephalogram (EEG) power spectra, sleep and motor activity have also been studied. (Kantor et al., Brain Research 943 (2002) 105-111) The studies by Kantor et al. showed that the 5HT2 receptor antagonist ritanserin has longterm effects on EEG power spectra, sleep and motility. Kantor et al. concluded that because ritanserin is a
- 10 5HT2 receptor antagonist, under physiological conditions, serotonin increases electroencephalogram (EEG) synchronization and produces an increase in vigilance level and motor activity by tonic activation of 5HT2 receptors. The proposed regulatory mechanism plays an important role in the waking process and the appearances of its effects in the light and dark phases were markedly different.
- 15 U.S. Patent Numbers 3,914,421; 4,013,652; 4,115,577; 4,183,936; and 4,238,607 disclose pyridopyrrolobenz-heterocycles of formula:



- 20 where X is O, S, S(=O), or SO₂; n is 0 or 1; R¹ is various carbon substituents, and Z is a monosubstituent of H, methyl, or chloro.

 U.S. Patent Number 4,219,550 discloses pyridopyrrolo-benzheterocycles of formula:



where X is O or S; R¹ is C₁₋₄ alkyl or cyclopropyl; R² is H, CH₃, OCH₃, Cl, Br, F, or CF₃; and (A) is -CH₂-, -CH(CH₃)-, or -CH₂CH₂-.

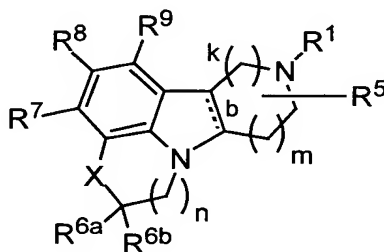
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SUMMARY OF THE INVENTION

One object of the present invention is to provide methods for treating central nervous system disorders including addictive behavior and sleep disorders, comprising administering to a host in need of such treatment a therapeutically effective amount of compounds which are useful as agonists or antagonists of 5-HT₂ receptors, more specifically 5-HT_{2A} and 5-HT_{2C} receptors, or pharmaceutically acceptable salts or prodrugs thereof.

This and other objects, which will become apparent during the following detailed description, have been achieved by the inventors' discovery that compounds of Formula (I):

15



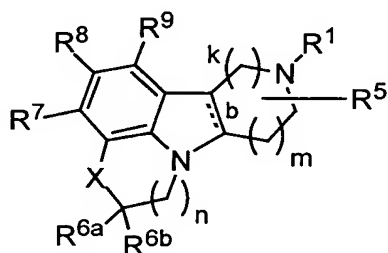
(I)

or pharmaceutically acceptable salt or prodrug forms thereof, wherein R¹, R⁵, R^{6a}, R^{6b}, R⁷, R⁸, R⁹, X, b, k, m, and n are defined below, are effective agonists or antagonists of 5-HT₂ receptors and can be used in the treatment of central nervous system disorders including addictive behavior and sleep disorders.

20

DETAILED DESCRIPTION OF THE EMBODIMENTS

Thus, in a first embodiment, the present invention provides a method for treating a human suffering from addictive behavior associated with 5HT2C receptor modulation, comprising administering to a patient in need thereof a therapeutically effective amount of a compound of formula (I):



(I)

or stereoisomers or pharmaceutically acceptable salt forms thereof, wherein:

b is a single bond;

X is -CHR¹⁰- or -C(=O)-;

15

R¹ is selected from

H,

C(=O)R²,

C(=O)OR²,

20

C₁₋₈ alkyl,

C₂₋₈ alkenyl,

C₂₋₈ alkynyl,

C₃₋₇ cycloalkyl,

C₁₋₆ alkyl substituted with Z,

25

C₂₋₆ alkenyl substituted with Z,

C₂₋₆ alkynyl substituted with Z,

C₃₋₆ cycloalkyl substituted with Z,
 aryl substituted with Z,
 5-6 membered heterocyclic ring system containing at least one heteroatom
 selected from the group consisting of N, O, and S, said heterocyclic
 5 ring system substituted with Z;
 C₁₋₃ alkyl substituted with Y,
 C₂₋₃ alkenyl substituted with Y,
 C₂₋₃ alkynyl substituted with Y,
 C₁₋₆ alkyl substituted with 0-2 R²,
 10 C₂₋₆ alkenyl substituted with 0-2 R²,
 C₂₋₆ alkynyl substituted with 0-2 R²,
 aryl substituted with 0-2 R², and
 5-6 membered heterocyclic ring system containing at least one heteroatom
 selected from the group consisting of N, O, and S, said heterocyclic
 15 ring system substituted with 0-2 R²;

Y is selected from

C₃₋₆ cycloalkyl substituted with Z,
 aryl substituted with Z,
 20 5-6 membered heterocyclic ring system containing at least one heteroatom
 selected from the group consisting of N, O, and S, said heterocyclic
 ring system substituted with Z;
 C₃₋₆ cycloalkyl substituted with -(C₁₋₃ alkyl)-Z,
 aryl substituted with -(C₁₋₃ alkyl)-Z, and
 25 5-6 membered heterocyclic ring system containing at least one heteroatom
 selected from the group consisting of N, O, and S, said heterocyclic
 ring system substituted with -(C₁₋₃ alkyl)-Z;

Z is selected from H,

30 -CH(OH)R²,

- 5 -C(ethylenedioxy)R²,
 -OR²,
 -SR²,
 -NR²R³,
 -C(O)R²,
 -C(O)NR²R³,
 -NR³C(O)R²,
 -C(O)OR²,
 -OC(O)R²,
 10 -CH(=NR⁴)NR²R³,
 -NHC(=NR⁴)NR²R³,
 -S(O)R²,
 -S(O)₂R²,
 -S(O)₂NR²R³, and -NR³S(O)₂R²;
 15 R², at each occurrence, is independently selected from
 halo,
 C₁₋₃ haloalkyl,
 C₁₋₄ alkyl,
 20 C₂₋₄ alkenyl,
 C₂₋₄ alkynyl,
 C₃₋₆ cycloalkyl,
 aryl substituted with 0-5 R⁴²;
 C₃₋₁₀ carbocyclic group substituted with 0-3 R⁴¹, and
 25 5-10 membered heterocyclic ring system containing from 1-4 heteroatoms
 selected from the group consisting of N, O, and S substituted with 0-3
 R⁴¹;

R³, at each occurrence, is independently selected from
H, C₁₋₄ alkyl, C₂₋₄ alkenyl, C₂₋₄ alkynyl, and
C₁₋₄ alkoxy;

- 5 alternatively, R² and R³ join to form a 5- or 6-membered ring optionally substituted
with -O- or -N(R⁴)-;

R⁴, at each occurrence, is independently selected from H and C₁₋₄ alkyl;

- 10 R⁵ is H or C₁₋₄ alkyl;

R^{6a} and R^{6b}, at each occurrence, are independently selected from
H, -OH, -NR⁴⁶R⁴⁷, -CF₃, C₁₋₄ alkyl, C₂₋₄ alkenyl, C₂₋₄ alkynyl, C₁₋₄
alkoxy, C₁₋₄ haloalkyl, C₃₋₆ cycloalkyl, and

- 15 aryl substituted with 0-3 R⁴⁴;

R⁷ and R⁹, at each occurrence, are independently selected from
H, halo, -CF₃, -OCF₃, -OH, -CN, -NO₂, -NR⁴⁶R⁴⁷,
C₁₋₈ alkyl, C₂₋₈ alkenyl, C₂₋₈ alkynyl, C₁₋₄ haloalkyl, C₁₋₈ alkoxy, (C₁₋₄
20 haloalkyl)oxy,

C₃₋₁₀ cycloalkyl substituted with 0-2 R³³,

C₁₋₄ alkyl substituted with 0-2 R¹¹,

C₃₋₁₀ carbocyclic group substituted with 0-3 R³³,

aryl substituted with 0-5 R³³,

- 25 5-10 membered heterocyclic ring system containing from 1-4 heteroatoms
selected from the group consisting of N, O, and S substituted with 0-3
R³¹;

OR¹², SR¹², NR¹²R¹³, C(O)H, C(O)R¹², C(O)NR¹²R¹³, NR¹⁴C(O)R¹²,
 C(O)OR¹², OC(O)R¹², OC(O)OR¹², CH(=NR¹⁴)NR¹²R¹³,
 NHC(=NR¹⁴)NR¹²R¹³, S(O)R¹², S(O)₂R¹², S(O)NR¹²R¹³,
 S(O)₂NR¹²R¹³, NR¹⁴S(O)R¹², NR¹⁴S(O)₂R¹², NR¹²C(O)R¹⁵,
 5 NR¹²C(O)OR¹⁵, NR¹²S(O)₂R¹⁵, and NR¹²C(O)NHR¹⁵;

R⁸ is selected from

H, halo, -CF₃, -OCF₃, -OH, -CN, -NO₂,
 C₁₋₈ alkyl, C₂₋₈ alkenyl, C₂₋₈ alkynyl, C₁₋₄ haloalkyl, C₁₋₈ alkoxy, (C₁₋₄
 10 haloalkyl)oxy,
 C₃₋₁₀ cycloalkyl substituted with 0-2 R³³,
 C₁₋₄ alkyl substituted with 0-2 R¹¹,
 C₂₋₄ alkenyl substituted with 0-2 R¹¹,
 C₂₋₄ alkynyl substituted with 0-1 R¹¹,
 15 C₃₋₁₀ carbocyclic group substituted with 0-3 R³³,
 aryl substituted with 0-5 R³³,
 5-10 membered heterocyclic ring system containing from 1-4 heteroatoms
 selected from the group consisting of N, O, and S substituted with 0-3
 R³¹;

20

OR¹², SR¹², NR¹²R¹³, C(O)H, C(O)R¹², C(O)NR¹²R¹³, NR¹⁴C(O)R¹²,
 C(O)OR¹², OC(O)R¹², OC(O)OR¹², CH(=NR¹⁴)NR¹²R¹³,
 NHC(=NR¹⁴)NR¹²R¹³, S(O)R¹², S(O)₂R¹², S(O)NR¹²R¹³,
 S(O)₂NR¹²R¹³, NR¹⁴S(O)R¹², NR¹⁴S(O)₂R¹², NR¹²C(O)R¹⁵,
 25 NR¹²C(O)OR¹⁵, NR¹²S(O)₂R¹⁵, and NR¹²C(O)NHR¹⁵;

R¹⁰ is selected from H, -OH,

C₁₋₆ alkyl substituted with 0-1 R^{10B},
 C₂₋₆ alkenyl substituted with 0-1 R^{10B},
 C₂₋₆ alkynyl substituted with 0-1 R^{10B}, and
 C₁₋₆ alkoxy;

5

R^{10B} is selected from

C₁₋₄ alkoxy,
 C₃₋₆ cycloalkyl,

10 C₃₋₁₀ carbocyclic group substituted with 0-3 R³³,
 phenyl substituted with 0-3 R³³, and
 5-6 membered heterocyclic ring system containing 1, 2, or 3 heteroatoms
 selected from the group consisting of N, O, and S substituted with 0-2
 R⁴⁴;

15 R¹¹ is selected from

H, halo, -CF₃, -CN, -NO₂,
 C₁₋₈ alkyl, C₂₋₈ alkenyl, C₂₋₈ alkynyl, C₁₋₄ haloalkyl, C₁₋₈ alkoxy, C₃₋₁₀
 cycloalkyl,

20 C₃₋₁₀ carbocyclic group substituted with 0-3 R³³,
 aryl substituted with 0-5 R³³,
 5-10 membered heterocyclic ring system containing from 1-4 heteroatoms
 selected from the group consisting of N, O, and S substituted with 0-3
 R³¹;

25 OR¹², SR¹², NR¹²R¹³, C(O)H, C(O)R¹², C(O)NR¹²R¹³, NR¹⁴C(O)R¹²,
 C(O)OR¹², OC(O)R¹², OC(O)OR¹², CH(=NR¹⁴)NR¹²R¹³,
 NHC(=NR¹⁴)NR¹²R¹³, S(O)R¹², S(O)₂R¹², S(O)NR¹²R¹³,

$S(O)_2NR^{12}R^{13}$, $NR^{14}S(O)R^{12}$, $NR^{14}S(O)_2R^{12}$, $NR^{12}C(O)R^{15}$,
 $NR^{12}C(O)OR^{15}$, $NR^{12}S(O)_2R^{15}$, and $NR^{12}C(O)NHR^{15}$;

R^{12} , at each occurrence, is independently selected from

- 5 C_{1-4} alkyl substituted with 0-1 R^{12a} ,
 C_{2-4} alkenyl substituted with 0-1 R^{12a} ,
 C_{2-4} alkynyl substituted with 0-1 R^{12a} ,
 C_{3-6} cycloalkyl substituted with 0-3 R^{33} ,
phenyl substituted with 0-5 R^{33} ;
- 10 C_{3-10} carbocyclic group substituted with 0-3 R^{33} , and
5-10 membered heterocyclic ring system containing from 1-4 heteroatoms
selected from the group consisting of N, O, and S substituted with 0-3
 R^{31} ;
- 15 R^{12a} , at each occurrence, is independently selected from
phenyl substituted with 0-5 R^{33} ;
 C_{3-10} carbocyclic group substituted with 0-3 R^{33} , and
5-10 membered heterocyclic ring system containing from 1-4 heteroatoms
selected from the group consisting of N, O, and S substituted with 0-3
20 R^{31} ;

R^{13} , at each occurrence, is independently selected from

H, C_{1-4} alkyl, C_{2-4} alkenyl, and C_{2-4} alkynyl;

- 25 alternatively, R^{12} and R^{13} join to form a 5- or 6-membered ring optionally
substituted with -O- or -N(R^{14})-;

alternatively, R¹² and R¹³ when attached to N may be combined to form a 9- or 10-membered bicyclic heterocyclic ring system containing from 1-3 heteroatoms selected from the group consisting of N, O, and S, wherein said bicyclic heterocyclic ring system is unsaturated or partially saturated, wherein said
 5 bicyclic heterocyclic ring system is substituted with 0-3 R¹⁶;

R¹⁴, at each occurrence, is independently selected from H and C₁₋₄ alkyl;

R¹⁵, at each occurrence, is independently selected from
 10 H, C₁₋₄ alkyl, C₂₋₄ alkenyl, and C₂₋₄ alkynyl;

R¹⁶, at each occurrence, is independently selected from
 H, OH, halo, CN, NO₂, CF₃, SO₂R⁴⁵, NR⁴⁶R⁴⁷, -C(=O)H,
 C₁₋₄ alkyl, C₂₋₄ alkenyl, C₂₋₄ alkynyl, C₁₋₄ haloalkyl,
 15 C₁₋₃ haloalkyl-oxy-, and C₁₋₃ alkyloxy-;

R³¹, at each occurrence, is independently selected from
 H, OH, halo, CF₃, SO₂R⁴⁵, NR⁴⁶R⁴⁷, and C₁₋₄ alkyl;

20 R³³, at each occurrence, is independently selected from
 H, OH, halo, CN, NO₂, CF₃, SO₂R⁴⁵, NR⁴⁶R⁴⁷, -C(=O)H,
 C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl,
 C₃₋₆ cycloalkyl, C₁₋₄ haloalkyl, C₁₋₄ haloalkyl-oxy-, C₁₋₄ alkyloxy-,
 C₁₋₄ alkylthio-, C₁₋₄ alkyl-C(=O)-, C₁₋₄ alkyl-C(=O)NH-, C₁₋₄ alkyl-
 25 OC(=O)-,
 C₁₋₄ alkyl-C(=O)O-, C₃₋₆ cycloalkyl-oxy-, C₃₋₆ cycloalkylmethyl-oxy-;
 C₁₋₆ alkyl substituted with OH, methoxy, ethoxy, propoxy, or butoxy; and
 C₂₋₆ alkenyl substituted with OH, methoxy, ethoxy, propoxy, or butoxy;

- R⁴¹, at each occurrence, is independently selected from
- H, CF₃, halo, OH, CO₂H, SO₂R⁴⁵, NR⁴⁶R⁴⁷, NO₂, CN, =O;
 - C₂₋₈ alkenyl, C₂₋₈ alkynyl, C₁₋₄ alkoxy, C₁₋₄ haloalkyl
 - C₁₋₄ alkyl substituted with 0-1 R⁴³,
 - 5 aryl substituted with 0-3 R⁴², and
 - 5-10 membered heterocyclic ring system containing from 1-4 heteroatoms
selected from the group consisting of N, O, and S substituted with 0-3
R⁴⁴;
- 10 R⁴², at each occurrence, is independently selected from
- H, CF₃, halo, OH, CO₂H, SO₂R⁴⁵, SO⁴⁵, SR⁴⁵, NR⁴⁶SO₂R⁴⁵,
 - NR⁴⁶COR⁴⁵, NR⁴⁶R⁴⁷, NO₂, CN, CH(=NH)NH₂, NHC(=NH)NH₂,
 - C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₁₋₄ alkoxy, C₁₋₄ haloalkyl, C₃₋₆ cycloalkyl,
 - C₁₋₄ alkyl substituted with 0-1 R⁴³,
 - 15 aryl substituted with 0-3 R⁴⁴, and
 - 5-10 membered heterocyclic ring system containing from 1-4 heteroatoms
selected from the group consisting of N, O, and S substituted with 0-3
R⁴⁴;
- 20 R⁴³ is C₃₋₆ cycloalkyl or aryl substituted with 0-3 R⁴⁴;
- R⁴⁴, at each occurrence, is independently selected from H, halo, -OH, NR⁴⁶R⁴⁷,
CO₂H, SO₂R⁴⁵, -CF₃, -OCF₃, -CN, -NO₂, C₁₋₄ alkyl, and C₁₋₄ alkoxy;
- 25 R⁴⁵ is C₁₋₄ alkyl;
- R⁴⁶, at each occurrence, is independently selected from H and C₁₋₄ alkyl;

R⁴⁷, at each occurrence, is independently selected from H, C₁₋₄ alkyl,

-C(=O)NH(C₁₋₄ alkyl), -SO₂(C₁₋₄ alkyl),

-C(=O)O(C₁₋₄ alkyl), -C(=O)(C₁₋₄ alkyl), and -C(=O)H;

5 k is 1 or 2;

m is 0, 1, or 2;

n is 0, 1, 2, or 3;

provided when m is 0 or 1 then k is 1 or 2;

10 provided when m is 2 then k is 1;

provided that when R⁶ or R^{6a} is NH₂, then X is not -CH(R¹⁰); and

provided that when n=0, then R⁶ or R^{6a} is not NH₂ or -OH.

15 In a preferred embodiment, the present invention provides the method as defined in Claim 1 where in the compound administered:

X is -CHR¹⁰- or -C(=O)-;

R¹ is selected from

20 H,

C(=O)R²,

C(=O)OR²,

C₁₋₈ alkyl,

C₂₋₈ alkenyl,

25 C₂₋₈ alkynyl,

C₃₋₇ cycloalkyl,

C₁₋₆ alkyl substituted with 0-2 R²,

C₂₋₆ alkenyl substituted with 0-2 R²,

C₂₋₆ alkynyl substituted with 0-2 R²,

aryl substituted with 0-2 R^2 , and
5-6 membered heterocyclic ring system containing at least one heteroatom
selected from the group consisting of N, O, and S, said heterocyclic
ring system substituted with 0-2 R^2 ;

5

R^2 , at each occurrence, is independently selected from

F, Cl, CH_2F , CHF_2 , CF_3 ,

C_{1-4} alkyl,

C_{2-4} alkenyl,

10 C_{2-4} alkynyl,

C_{3-6} cycloalkyl,

phenyl substituted with 0-5 R^{42} ;

C_{3-10} carbocyclic group substituted with 0-3 R^{41} , and

5-10 membered heterocyclic ring system containing from 1-4 heteroatoms

15 selected from the group consisting of N, O, and S substituted with 0-3
 R^{41} ;

R^5 is H, methyl, ethyl, propyl, or butyl;

20 R^{6a} is selected from

H, -OH, $-NR^{46}R^{47}$, $-CF_3$,

C_{1-4} alkyl, C_{1-4} alkoxy, C_{1-4} haloalkyl, and

aryl substituted with 0-3 R^{44} ;

25 R^{6b} is H;

R^7 and R^9 , at each occurrence, are independently selected from

H, halo, $-CF_3$, $-OCF_3$, -OH, -CN, $-NO_2$, $-NR^{46}R^{47}$,

C₁₋₈ alkyl, C₂₋₈ alkenyl, C₂₋₈ alkynyl, C₁₋₄ haloalkyl, C₁₋₈ alkoxy, (C₁₋₄ haloalkyl)oxy,
 C₃₋₁₀ cycloalkyl substituted with 0-2 R³³,
 C₁₋₄ alkyl substituted with 0-2 R¹¹,
 5 C₃₋₁₀ carbocyclic group substituted with 0-3 R³³,
 aryl substituted with 0-5 R³³,
 5-10 membered heterocyclic ring system containing from 1-4 heteroatoms
 selected from the group consisting of N, O, and S substituted with 0-3
 R³¹;
 10
 OR¹², SR¹², NR¹²R¹³, C(O)H, C(O)R¹², C(O)NR¹²R¹³, NR¹⁴C(O)R¹²,
 C(O)OR¹², OC(O)R¹², OC(O)OR¹², CH(=NR¹⁴)NR¹²R¹³,
 NHC(=NR¹⁴)NR¹²R¹³, S(O)R¹², S(O)₂R¹², S(O)NR¹²R¹³,
 S(O)₂NR¹²R¹³, NR¹⁴S(O)R¹², NR¹⁴S(O)₂R¹², NR¹²C(O)R¹⁵,
 15 NR¹²C(O)OR¹⁵, NR¹²S(O)₂R¹⁵, and NR¹²C(O)NHR¹⁵;

R⁸ is selected from

H, halo, -CF₃, -OCF₃, -OH, -CN, -NO₂,
 C₁₋₈ alkyl, C₂₋₈ alkenyl, C₂₋₈ alkynyl, C₁₋₄ haloalkyl, C₁₋₈ alkoxy, (C₁₋₄
 20 haloalkyl)oxy,
 C₃₋₁₀ cycloalkyl substituted with 0-2 R³³,
 C₁₋₄ alkyl substituted with 0-2 R¹¹,
 C₂₋₄ alkenyl substituted with 0-2 R¹¹,
 C₂₋₄ alkynyl substituted with 0-1 R¹¹,
 25 C₃₋₁₀ carbocyclic group substituted with 0-3 R³³,
 aryl substituted with 0-5 R³³,

5-10 membered heterocyclic ring system containing from 1-4 heteroatoms
selected from the group consisting of N, O, and S substituted with 0-3
R³¹;

5 OR¹², SR¹², NR¹²R¹³, C(O)H, C(O)R¹², C(O)NR¹²R¹³, NR¹⁴C(O)R¹²,
C(O)OR¹², OC(O)R¹², OC(O)OR¹², CH(=NR¹⁴)NR¹²R¹³,
NHC(=NR¹⁴)NR¹²R¹³, S(O)R¹², S(O)₂R¹², S(O)NR¹²R¹³,
S(O)₂NR¹²R¹³, NR¹⁴S(O)R¹², NR¹⁴S(O)₂R¹², NR¹²C(O)R¹⁵,
NR¹²C(O)OR¹⁵, NR¹²S(O)₂R¹⁵, and NR¹²C(O)NHR¹⁵;

10

R¹⁰ is selected from H, -OH,

C₁₋₆ alkyl substituted with 0-1 R^{10B},

C₂₋₆ alkenyl substituted with 0-1 R^{10B},

C₂₋₆ alkynyl substituted with 0-1 R^{10B}, and

15

C₁₋₆ alkoxy;

R^{10B} is selected from

C₁₋₄ alkoxy,

C₃₋₆ cycloalkyl,

20

C₃₋₁₀ carbocyclic group substituted with 0-3 R³³,

phenyl substituted with 0-3 R³³, and

5-6 membered heterocyclic ring system containing 1, 2, or 3 heteroatoms
selected from the group consisting of N, O, and S substituted with 0-2
R⁴⁴;

25

R¹¹ is selected from

H, halo, -CF₃, -CN, -NO₂,

- C₁₋₈ alkyl, C₂₋₈ alkenyl, C₂₋₈ alkynyl, C₁₋₄ haloalkyl, C₁₋₈ alkoxy, C₃₋₁₀ cycloalkyl,
 C₃₋₁₀ carbocyclic group substituted with 0-3 R³³,
 aryl substituted with 0-5 R³³,
 5 5-10 membered heterocyclic ring system containing from 1-4 heteroatoms
 selected from the group consisting of N, O, and S substituted with 0-3
 R³¹;
- OR¹², SR¹², NR¹²R¹³, C(O)H, C(O)R¹², C(O)NR¹²R¹³, NR¹⁴C(O)R¹²,
 10 C(O)OR¹², OC(O)R¹², OC(O)OR¹², CH(=NR¹⁴)NR¹²R¹³,
 NHC(=NR¹⁴)NR¹²R¹³, S(O)R¹², S(O)₂R¹², S(O)NR¹²R¹³,
 S(O)₂NR¹²R¹³, NR¹⁴S(O)R¹², NR¹⁴S(O)₂R¹², NR¹²C(O)R¹⁵,
 NR¹²C(O)OR¹⁵, NR¹²S(O)₂R¹⁵, and NR¹²C(O)NHR¹⁵;
- 15 R¹², at each occurrence, is independently selected from
 C₁₋₄ alkyl substituted with 0-1 R^{12a},
 C₂₋₄ alkenyl substituted with 0-1 R^{12a},
 C₂₋₄ alkynyl substituted with 0-1 R^{12a},
 C₃₋₆ cycloalkyl substituted with 0-3 R³³,
 20 phenyl substituted with 0-5 R³³;
 C₃₋₁₀ carbocyclic group substituted with 0-3 R³³, and
 5-10 membered heterocyclic ring system containing from 1-4 heteroatoms
 selected from the group consisting of N, O, and S substituted with 0-3
 R³¹;
- 25 R^{12a}, at each occurrence, is independently selected from
 phenyl substituted with 0-5 R³³;
 C₃₋₁₀ carbocyclic group substituted with 0-3 R³³, and

5-10 membered heterocyclic ring system containing from 1-4 heteroatoms
selected from the group consisting of N, O, and S substituted with 0-3
R³¹;

5 R¹³, at each occurrence, is independently selected from
H, C₁₋₄ alkyl, C₂₋₄ alkenyl, and C₂₋₄ alkynyl;

alternatively, R¹² and R¹³ join to form a 5- or 6-membered ring optionally
substituted with -O- or -N(R¹⁴)-;

10

alternatively, R¹² and R¹³ when attached to N may be combined to form a 9- or 10-
membered bicyclic heterocyclic ring system containing from 1-3 heteroatoms
selected from the group consisting of N, O, and S, wherein said bicyclic
heterocyclic ring system is unsaturated or partially saturated, wherein said
15 bicyclic heterocyclic ring system is substituted with 0-3 R¹⁶;

R¹⁴, at each occurrence, is independently selected from H and C₁₋₄ alkyl;

20 R¹⁵, at each occurrence, is independently selected from
H, C₁₋₄ alkyl, C₂₋₄ alkenyl, and C₂₋₄ alkynyl;

R¹⁶, at each occurrence, is independently selected from
H, OH, halo, CN, NO₂, CF₃, SO₂R⁴⁵, NR⁴⁶R⁴⁷, -C(=O)H,
C₁₋₄ alkyl, C₂₋₄ alkenyl, C₂₋₄ alkynyl, C₁₋₄ haloalkyl,
25 C₁₋₃ haloalkyl-oxy-, and C₁₋₃ alkyloxy-;

R³¹, at each occurrence, is independently selected from
H, OH, halo, CF₃, SO₂R⁴⁵, NR⁴⁶R⁴⁷, and C₁₋₄ alkyl;

R³³, at each occurrence, is independently selected from

- H, OH, halo, CN, NO₂, CF₃, SO₂R⁴⁵, NR⁴⁶R⁴⁷, -C(=O)H,
 C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl,
 C₃₋₆ cycloalkyl, C₁₋₄ haloalkyl, C₁₋₄ haloalkyl-oxy-, C₁₋₄ alkyloxy-,
 5 C₁₋₄ alkylthio-, C₁₋₄ alkyl-C(=O)-, C₁₋₄ alkyl-C(=O)NH-, C₁₋₄ alkyl-
 OC(=O)-,
 C₁₋₄ alkyl-C(=O)O-, C₃₋₆ cycloalkyl-oxy-, C₃₋₆ cycloalkylmethyl-oxy-;
 C₁₋₆ alkyl substituted with OH, methoxy, ethoxy, propoxy, or butoxy; and
 C₂₋₆ alkenyl substituted with OH, methoxy, ethoxy, propoxy, or butoxy;

10

R⁴¹, at each occurrence, is independently selected from

- H, CF₃, halo, OH, CO₂H, SO₂R⁴⁵, NR⁴⁶R⁴⁷, NO₂, CN;
 C₂₋₈ alkenyl, C₂₋₈ alkynyl, C₁₋₄ alkoxy, C₁₋₄ haloalkyl
 C₁₋₄ alkyl substituted with 0-1 R⁴³,
 15 aryl substituted with 0-3 R⁴², and
 5-10 membered heterocyclic ring system containing from 1-4 heteroatoms
 selected from the group consisting of N, O, and S substituted with 0-3
 R⁴⁴;

20 R⁴², at each occurrence, is independently selected from

- H, CF₃, halo, OH, CO₂H, SO₂R⁴⁵, NR⁴⁶R⁴⁷, NO₂, CN, CH(=NH)NH₂,
 NHC(=NH)NH₂,
 C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₁₋₄ alkoxy, C₁₋₄ haloalkyl, C₃₋₆ cycloalkyl,
 C₁₋₄ alkyl substituted with 0-1 R⁴³,
 25 aryl substituted with 0-3 R⁴⁴, and
 5-10 membered heterocyclic ring system containing from 1-4 heteroatoms
 selected from the group consisting of N, O, and S substituted with 0-3
 R⁴⁴;

R⁴³ is C₃₋₆ cycloalkyl or aryl substituted with 0-3 R⁴⁴;

R⁴⁴, at each occurrence, is independently selected from H, halo, -OH, NR⁴⁶R⁴⁷,
CO₂H, SO₂R⁴⁵, -CF₃, -OCF₃, -CN, -NO₂, C₁₋₄ alkyl, and C₁₋₄ alkoxy;

5

R⁴⁵ is C₁₋₄ alkyl;

R⁴⁶, at each occurrence, is independently selected from H and C₁₋₄ alkyl;

10 R⁴⁷, at each occurrence, is independently selected from H and C₁₋₄ alkyl;

k is 1 or 2;

m is 0, 1, or 2; and

n is 0, 1, 2, or 3.

15

In a more preferred embodiment, the present invention provides the method as defined in Claim 2 where in the compound administered:

20 X is -CHR¹⁰-;

R¹ is selected from

H,

C(=O)R²,

25 C(=O)OR²,

C₁₋₆ alkyl,

C₂₋₆ alkenyl,

C₂₋₆ alkynyl,

C₃₋₆ cycloalkyl,

C₁₋₄ alkyl substituted with 0-2 R²,
C₂₋₄ alkenyl substituted with 0-2 R², and
C₂₋₄ alkynyl substituted with 0-2 R²;

5 R², at each occurrence, is independently selected from

C₁₋₄ alkyl,
C₂₋₄ alkenyl,
C₂₋₄ alkynyl,
C₃₋₆ cycloalkyl,

10 phenyl substituted with 0-5 R⁴²;

C₃₋₁₀ carbocyclic group substituted with 0-3 R⁴¹, and

5-10 membered heterocyclic ring system containing from 1-4 heteroatoms
selected from the group consisting of N, O, and S substituted with 0-3
R⁴¹;

15

R⁵ is H, methyl, ethyl, propyl, or butyl;

R^{6a} is selected independently from

H, -OH, -NR⁴⁶R⁴⁷, -CF₃, C₁₋₃ alkyl, and C₁₋₃ alkoxy;

20

R^{6b} is H;

R⁷ and R⁹, at each occurrence, are independently selected from

H, halo, -CF₃, -OCF₃, -OH, -CN, -NO₂, -NR⁴⁶R⁴⁷,

25 C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₁₋₆ haloalkyl, C₁₋₆ alkoxy, (C₁₋₄
haloalkyl)oxy,

C₃₋₁₀ cycloalkyl substituted with 0-2 R³³,

C₁₋₄ alkyl substituted with 0-2 R¹¹,

5 C₃₋₁₀ carbocyclic group substituted with 0-3 R³³,
 aryl substituted with 0-5 R³³,
 5-10 membered heterocyclic ring system containing from 1-4 heteroatoms
 selected from the group consisting of N, O, and S substituted with 0-3
 R³¹;

OR¹², SR¹², NR¹²R¹³, C(O)H, C(O)R¹², C(O)NR¹²R¹³, NR¹⁴C(O)R¹²,
 C(O)OR¹², OC(O)R¹², OC(O)OR¹², CH(=NR¹⁴)NR¹²R¹³,
 NHC(=NR¹⁴)NR¹²R¹³, S(O)R¹², S(O)₂R¹², S(O)NR¹²R¹³,
 10 S(O)₂NR¹²R¹³, NR¹⁴S(O)R¹², and NR¹⁴S(O)₂R¹²;

R⁸ is selected from

H, halo, -CF₃, -OCF₃, -OH, -CN, -NO₂,
 C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₁₋₆ haloalkyl, C₁₋₆ alkoxy, (C₁₋₄
 15 haloalkyl)oxy,
 C₃₋₁₀ cycloalkyl substituted with 0-2 R³³,
 C₁₋₄ alkyl substituted with 0-2 R¹¹,
 C₂₋₄ alkenyl substituted with 0-2 R¹¹,
 C₂₋₄ alkynyl substituted with 0-1 R¹¹,
 20 C₃₋₁₀ carbocyclic group substituted with 0-3 R³³,
 aryl substituted with 0-5 R³³,
 5-10 membered heterocyclic ring system containing from 1-4 heteroatoms
 selected from the group consisting of N, O, and S substituted with 0-3
 R³¹;

25 OR¹², SR¹², NR¹²R¹³, C(O)H, C(O)R¹², C(O)NR¹²R¹³, NR¹⁴C(O)R¹²,
 C(O)OR¹², OC(O)R¹², OC(O)OR¹², CH(=NR¹⁴)NR¹²R¹³,
 NHC(=NR¹⁴)NR¹²R¹³, S(O)R¹², S(O)₂R¹², S(O)NR¹²R¹³,

$S(O)_2NR^{12}R^{13}$, $NR^{14}S(O)R^{12}$, $NR^{14}S(O)_2R^{12}$, $NR^{12}C(O)R^{15}$,
 $NR^{12}C(O)OR^{15}$, $NR^{12}S(O)_2R^{15}$, and $NR^{12}C(O)NHR^{15}$;

R^{10} is selected from H, -OH,

- 5 C_{1-6} alkyl substituted with 0-1 R^{10B} ,
 C_{2-6} alkenyl substituted with 0-1 R^{10B} ,
 C_{2-6} alkynyl substituted with 0-1 R^{10B} , and
 C_{1-6} alkoxy;

10 R^{10B} is selected from

- C_{1-4} alkoxy,
 C_{3-6} cycloalkyl,
 C_{3-10} carbocyclic group substituted with 0-3 R^{33} ,
 phenyl substituted with 0-3 R^{33} , and
 15 5-6 membered heterocyclic ring system containing 1, 2, or 3 heteroatoms
 selected from the group consisting of N, O, and S substituted with 0-2
 R^{44} ;

R^{11} is selected from

- 20 H, halo, -CF₃, -CN, -NO₂, C_{1-6} alkyl,
 C_{2-6} alkenyl, C_{2-6} alkynyl, C_{1-4} haloalkyl, C_{1-6} alkoxy, C_{3-10} cycloalkyl,
 C_{3-10} carbocyclic group substituted with 0-3 R^{33} ,
 aryl substituted with 0-5 R^{33} ,
 5-10 membered heterocyclic ring system containing from 1-4 heteroatoms
 25 selected from the group consisting of N, O, and S substituted with 0-3
 R^{31} ;

OR¹², SR¹², NR¹²R¹³, C(O)H, C(O)R¹², C(O)NR¹²R¹³, NR¹⁴C(O)R¹²,
 C(O)OR¹², OC(O)R¹², OC(O)OR¹², CH(=NR¹⁴)NR¹²R¹³,
 NHC(=NR¹⁴)NR¹²R¹³, S(O)R¹², S(O)₂R¹², S(O)NR¹²R¹³,
 S(O)₂NR¹²R¹³, NR¹⁴S(O)R¹², and NR¹⁴S(O)₂R¹²;

5

R¹², at each occurrence, is independently selected from

C₁₋₄ alkyl substituted with 0-1 R^{12a},

C₂₋₄ alkenyl substituted with 0-1 R^{12a},

C₂₋₄ alkynyl substituted with 0-1 R^{12a},

10 C₃₋₆ cycloalkyl substituted with 0-3 R³³,

phenyl substituted with 0-5 R³³;

C₃₋₁₀ carbocyclic group substituted with 0-3 R³³, and

5-10 membered heterocyclic ring system containing from 1-4 heteroatoms

selected from the group consisting of N, O, and S substituted with 0-3

15 R³¹;

R^{12a}, at each occurrence, is independently selected from

phenyl substituted with 0-5 R³³;

C₃₋₁₀ carbocyclic group substituted with 0-3 R³³, and

20 5-10 membered heterocyclic ring system containing from 1-4 heteroatoms

selected from the group consisting of N, O, and S substituted with 0-3

R³¹;

R¹³, at each occurrence, is independently selected from

25 H, C₁₋₄ alkyl, C₂₋₄ alkenyl, and C₂₋₄ alkynyl;

alternatively, R¹² and R¹³ join to form a 5- or 6-membered ring optionally

substituted with -O- or -N(R¹⁴)-;

alternatively, R¹² and R¹³ when attached to N may be combined to form a 9- or 10-
 membered bicyclic heterocyclic ring system containing from 1-3 heteroatoms
 selected from the group consisting of N, O, and S, wherein said bicyclic
 5 heterocyclic ring system is unsaturated or partially saturated, wherein said
 bicyclic heterocyclic ring system is substituted with 0-3 R¹⁶;

R¹⁴, at each occurrence, is independently selected from H, methyl, ethyl, propyl, and
 butyl;

10 R¹⁵, at each occurrence, is independently selected from
 H, C₁₋₄ alkyl, C₂₋₄ alkenyl, and C₂₋₄ alkynyl;

R¹⁶, at each occurrence, is independently selected from
 15 H, OH, F, Cl, CN, NO₂, CF₃, SO₂R⁴⁵, NR⁴⁶R⁴⁷, -C(=O)H,
 methyl, ethyl, methoxy, ethoxy, trifluoromethyl, and trifluoromethoxy;

R³¹, at each occurrence, is independently selected from
 H, OH, halo, CF₃, SO₂R⁴⁵, NR⁴⁶R⁴⁷, and C₁₋₄ alkyl;

20 R³³, at each occurrence, is independently selected from
 H, OH, halo, CN, NO₂, CF₃, SO₂R⁴⁵, NR⁴⁶R⁴⁷, -C(=O)H,
 C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl,
 C₃₋₆ cycloalkyl, C₁₋₄ haloalkyl, C₁₋₄ haloalkyl-oxy-, C₁₋₄ alkyloxy-,
 25 C₁₋₄ alkylthio-, C₁₋₄ alkyl-C(=O)-, C₁₋₄ alkyl-C(=O)NH-, C₁₋₄ alkyl-
 OC(=O)-,
 C₁₋₄ alkyl-C(=O)O-, C₃₋₆ cycloalkyl-oxy-, C₃₋₆ cycloalkylmethyl-oxy-;
 C₁₋₆ alkyl substituted with OH, methoxy, ethoxy, propoxy, or butoxy; and
 C₂₋₆ alkenyl substituted with OH, methoxy, ethoxy, propoxy, or butoxy;

R⁴¹, at each occurrence, is independently selected from

H, CF₃, halo, OH, CO₂H, SO₂R⁴⁵, NR⁴⁶R⁴⁷, NO₂, CN,

C₂₋₈ alkenyl, C₂₋₈ alkynyl, C₁₋₄ alkoxy, C₁₋₄ haloalkyl

5 C₁₋₄ alkyl substituted with 0-1 R⁴³,

aryl substituted with 0-3 R⁴², and

5-10 membered heterocyclic ring system containing from 1-4 heteroatoms

selected from the group consisting of N, O, and S substituted with 0-3
R⁴⁴;

10

R⁴², at each occurrence, is independently selected from

H, CF₃, halo, OH, CO₂H, SO₂R⁴⁵, NR⁴⁶R⁴⁷, NO₂, CN, CH(=NH)NH₂,

NHC(=NH)NH₂,

C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₁₋₄ alkoxy, C₁₋₄ haloalkyl, C₃₋₆ cycloalkyl,

15 C₁₋₄ alkyl substituted with 0-1 R⁴³,

aryl substituted with 0-3 R⁴⁴, and

5-10 membered heterocyclic ring system containing from 1-4 heteroatoms

selected from the group consisting of N, O, and S substituted with 0-3
R⁴⁴;

20

R⁴³ is C₃₋₆ cycloalkyl or aryl substituted with 0-3 R⁴⁴;

R⁴⁴, at each occurrence, is independently selected from H, halo, -OH, NR⁴⁶R⁴⁷,

CO₂H, SO₂R⁴⁵, -CF₃, -OCF₃, -CN, -NO₂, C₁₋₄ alkyl, and C₁₋₄ alkoxy;

25

R⁴⁵ is C₁₋₄ alkyl;

R⁴⁶, at each occurrence, is independently selected from H and C₁₋₄ alkyl;

R⁴⁷, at each occurrence, is independently selected from H and C₁₋₄ alkyl;

k is 1 or 2;

5 m is 0 or 1; and

n is 0, 1 or 2.

In a more preferred embodiment, the present invention provides the method as
10 defined in Claim 2 where in the compound administered:

X is -CH₂-;

R¹ is selected from

15 H,
C₁₋₄ alkyl,
C₂₋₄ alkenyl,
C₂₋₄ alkynyl,
C₃₋₄ cycloalkyl,
20 C₁₋₃ alkyl substituted with 0-1 R²,
C₂₋₃ alkenyl substituted with 0-1 R², and
C₂₋₃ alkynyl substituted with 0-1 R²;

R², at each occurrence, is independently selected from

25 C₁₋₄ alkyl,
C₂₋₄ alkenyl,
C₂₋₄ alkynyl,
C₃₋₆ cycloalkyl,
phenyl substituted with 0-5 R⁴²;

C₃₋₆ carbocyclic group substituted with 0-3 R⁴¹, and
5-6 membered heterocyclic ring system containing 1, 2, or 3 heteroatoms
selected from the group consisting of N, O, and S substituted with 0-3
R⁴¹;

5

R⁵ is H, methyl, ethyl, propyl, or butyl;

R^{6a} is H, methyl, ethyl, methoxy, -OH, or -CF₃;

10 R^{6b} is H;

R⁷ and R⁹, at each occurrence, are independently selected from

H, halo, -CF₃, -OCF₃, -OH, -CN, -NO₂, -NR⁴⁶R⁴⁷,

C₁₋₄ alkyl, C₂₋₄ alkenyl, C₂₋₄ alkynyl, C₁₋₄ haloalkyl, C₁₋₄ alkoxy, (C₁₋₄
15 haloalkyl)oxy,

C₃₋₁₀ cycloalkyl substituted with 0-2 R³³,

C₁₋₄ alkyl substituted with 0-2 R¹¹,

C₃₋₁₀ carbocyclic group substituted with 0-3 R³³,

aryl substituted with 0-5 R³³, and

20 5-6 membered heterocyclic ring system containing 1, 2, or 3 heteroatoms
selected from the group consisting of N, O, and S substituted with 0-3
R³¹;

R⁸ is selected from

25 H, halo, -CF₃, -OCF₃, -OH, -CN, -NO₂,

C₁₋₄ alkyl, C₂₋₄ alkenyl, C₂₋₄ alkynyl, C₁₋₄ haloalkyl, C₁₋₄ alkoxy, (C₁₋₄
haloalkyl)oxy,

C₃₋₁₀ cycloalkyl substituted with 0-2 R³³,

C₁₋₄ alkyl substituted with 0-2 R¹¹,
 C₂₋₄ alkenyl substituted with 0-2 R¹¹,
 C₂₋₄ alkynyl substituted with 0-1 R¹¹,
 C₃₋₁₀ carbocyclic group substituted with 0-3 R³³,
 5 aryl substituted with 0-5 R³³,
 5-6 membered heterocyclic ring system containing 1, 2, or 3 heteroatoms
 selected from the group consisting of N, O, and S substituted with 0-3
 R³¹;
 OR¹², SR¹², NR¹²R¹³, NR¹²C(O)R¹⁵, NR¹²C(O)OR¹⁵, NR¹²S(O)₂R¹⁵,
 10 and NR¹²C(O)NHR¹⁵;

R¹¹ is selected from
 H, halo, -CF₃, -CN, -NO₂,
 C₁₋₄ alkyl, C₂₋₄ alkenyl, C₂₋₄ alkynyl, C₁₋₄ haloalkyl, C₁₋₄ alkoxy, (C₁₋₄
 15 haloalkyl)oxy,
 C₃₋₁₀ cycloalkyl substituted with 0-2 R³³,
 C₃₋₁₀ carbocyclic group substituted with 0-3 R³³,
 aryl substituted with 0-5 R³³, and
 5-6 membered heterocyclic ring system containing 1, 2, or 3 heteroatoms
 20 selected from the group consisting of N, O, and S substituted with 0-3
 R³¹;

R¹², at each occurrence, is independently selected from
 C₁₋₄ alkyl substituted with 0-1 R^{12a},
 25 C₂₋₄ alkenyl substituted with 0-1 R^{12a},
 C₂₋₄ alkynyl substituted with 0-1 R^{12a},
 C₃₋₆ cycloalkyl substituted with 0-3 R³³,
 phenyl substituted with 0-5 R³³;

C₃₋₁₀ carbocyclic group substituted with 0-3 R³³, and
 5-10 membered heterocyclic ring system containing from 1-4 heteroatoms
 selected from the group consisting of N, O, and S substituted with 0-3
 R³¹;

5

R^{12a}, at each occurrence, is independently selected from
 phenyl substituted with 0-5 R³³;

C₃₋₁₀ carbocyclic group substituted with 0-3 R³³, and

5-10 membered heterocyclic ring system containing from 1-4 heteroatoms

10 selected from the group consisting of N, O, and S substituted with 0-3
 R³¹;

R¹³, at each occurrence, is independently selected from
 H, C₁₋₄ alkyl, C₂₋₄ alkenyl, and C₂₋₄ alkynyl;

15

alternatively, R¹² and R¹³ join to form a 5- or 6-membered ring optionally
 substituted with -O- or -N(R¹⁴)-;

alternatively, R¹² and R¹³ when attached to N may be combined to form a 9- or 10-
 20 membered bicyclic heterocyclic ring system containing from 1-3 heteroatoms
 selected from the group consisting of one N, two N, three N, one N one O, and
 one N one S; wherein said bicyclic heterocyclic ring system is unsaturated or
 partially saturated, wherein said bicyclic heterocyclic ring system is substituted
 with 0-2 R¹⁶;

25

R¹⁴, at each occurrence, is independently selected from H, methyl, ethyl, propyl, and
 butyl;

R¹⁵, at each occurrence, is independently selected from H, methyl, ethyl, propyl, and
 30 butyl;

R¹⁶, at each occurrence, is independently selected from

H, OH, F, Cl, CN, NO₂, methyl, ethyl, methoxy, ethoxy, trifluoromethyl, and trifluoromethoxy;

5

R³¹, at each occurrence, is independently selected from

H, OH, halo, CF₃, methyl, ethyl, and propyl;

R³³, at each occurrence, is independently selected from

10 H, OH, halo, CN, NO₂, CF₃, SO₂R⁴⁵, NR⁴⁶R⁴⁷, -C(=O)H,
C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl,
C₃₋₆ cycloalkyl, C₁₋₄ haloalkyl, C₁₋₄ haloalkyl-oxy-, C₁₋₄ alkyloxy-,
C₁₋₄ alkylthio-, C₁₋₄ alkyl-C(=O)-, C₁₋₄ alkyl-C(=O)NH-, C₁₋₄ alkyl-
OC(=O)-,
15 C₁₋₄ alkyl-C(=O)O-, C₃₋₆ cycloalkyl-oxy-, C₃₋₆ cycloalkylmethyl-oxy-;
C₁₋₆ alkyl substituted with OH, methoxy, ethoxy, propoxy, or butoxy; and
C₂₋₆ alkenyl substituted with OH, methoxy, ethoxy, propoxy, or butoxy;

R⁴¹, at each occurrence, is independently selected from

20 H, CF₃, halo, OH, CO₂H, SO₂R⁴⁵, NR⁴⁶R⁴⁷, NO₂, CN,
C₂₋₄ alkenyl, C₂₋₄ alkynyl, C₁₋₃ alkoxy, C₁₋₃ haloalkyl, and C₁₋₃ alkyl;

R⁴², at each occurrence, is independently selected from

25 H, CF₃, halo, OH, CO₂H, SO₂R⁴⁵, NR⁴⁶R⁴⁷, NO₂, CN, CH(=NH)NH₂,
NHC(=NH)NH₂,
C₂₋₄ alkenyl, C₂₋₄ alkynyl, C₁₋₃ alkoxy, C₁₋₃ haloalkyl, C₃₋₆ cycloalkyl, and
C₁₋₃ alkyl;

R⁴³ is cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, phenyl, or pyridyl, each substituted with 0-3 R⁴⁴;

R⁴⁴, at each occurrence, is independently selected from H, halo, -OH, NR⁴⁶R⁴⁷,
5 CO₂H, SO₂R⁴⁵, -CF₃, -OCF₃, -CN, -NO₂, methyl, ethyl, propyl, butyl,
methoxy, ethoxy, propoxy, and butoxy;

R⁴⁵ is methyl, ethyl, propyl, or butyl;

10 R⁴⁶, at each occurrence, is independently selected from H, methyl, ethyl, propyl, and
butyl;

R⁴⁷, at each occurrence, is independently selected from from H, methyl, ethyl, propyl,
and butyl;

15

k is 1;
m is 1; and
n is 0, 1 or 2.

20

In a more preferred embodiment, the present invention provides the method as
defined in Claim 2 where in the compound administered:

X is -CH₂-;

25

R¹ is selected from

H,

C₁₋₄ alkyl,

C₂₋₄ alkenyl,

30

C₂₋₄ alkynyl,

C₃₋₄ cycloalkyl,
C₁₋₃ alkyl substituted with 0-1 R²,
C₂₋₃ alkenyl substituted with 0-1 R², and
C₂₋₃ alkynyl substituted with 0-1 R²;

5

R², at each occurrence, is independently selected from

C₁₋₄ alkyl,
C₂₋₄ alkenyl,
C₂₋₄ alkynyl,
10 C₃₋₆ cycloalkyl,
phenyl substituted with 0-5 R⁴²;
C₃₋₆ carbocyclic group substituted with 0-3 R⁴¹, and
5-6 membered heterocyclic ring system containing 1, 2, or 3 heteroatoms
selected from the group consisting of N, O, and S substituted with 0-3
15 R⁴¹;

R⁵ is H, methyl, ethyl, propyl, or butyl;

R^{6a} is H, methyl, ethyl, methoxy, -OH, or -CF₃;

20

R^{6b} is H;

R⁷ and R⁹, at each occurrence, are independently selected from
H, F, Cl, -CH₃, -OCH₃, -CF₃, -OCF₃, -CN, and -NO₂,

25

R⁸ is selected from

H, F, Cl, Br, -CF₃, -OCF₃, -OH, -CN, -NO₂,
C₁₋₄ alkyl, C₂₋₄ alkenyl, C₂₋₄ alkynyl, C₁₋₄ haloalkyl, C₁₋₄ alkoxy, (C₁₋₄
haloalkyl)oxy,

- C₃₋₁₀ cycloalkyl substituted with 0-2 R³³,
 C₁₋₄ alkyl substituted with 0-2 R¹¹,
 C₂₋₄ alkenyl substituted with 0-2 R¹¹,
 C₂₋₄ alkynyl substituted with 0-1 R¹¹,
 5 C₃₋₁₀ carbocyclic group substituted with 0-3 R³³,
 aryl substituted with 0-5 R³³,
 5-6 membered heterocyclic ring system containing 1, 2, or 3 heteroatoms
 selected from the group consisting of N, O, and S substituted with 0-3
 R³¹;
 10 OR¹², SR¹², NR¹²R¹³, NR¹²C(O)R¹⁵, NR¹²C(O)OR¹⁵, NR¹²S(O)₂R¹⁵,
 and NR¹²C(O)NHR¹⁵;

R¹¹ is selected from

- H, halo, -CF₃, -CN, -NO₂,
 15 C₁₋₄ alkyl, C₂₋₄ alkenyl, C₂₋₄ alkynyl, C₁₋₄ haloalkyl, C₁₋₄ alkoxy, (C₁₋₄
 haloalkyl)oxy,
 C₃₋₁₀ cycloalkyl substituted with 0-2 R³³,
 C₃₋₁₀ carbocyclic group substituted with 0-3 R³³,
 aryl substituted with 0-5 R³³, and
 20 5-6 membered heterocyclic ring system containing 1, 2, or 3 heteroatoms
 selected from the group consisting of N, O, and S substituted with 0-3
 R³¹;

R¹², at each occurrence, is independently selected from

- 25 C₁₋₄ alkyl substituted with 0-1 R^{12a},
 C₂₋₄ alkenyl substituted with 0-1 R^{12a},
 C₂₋₄ alkynyl substituted with 0-1 R^{12a},
 C₃₋₆ cycloalkyl substituted with 0-3 R³³,

phenyl substituted with 0-5 R³³;
 C₃₋₁₀ carbocyclic group substituted with 0-3 R³³, and
 5-10 membered heterocyclic ring system containing from 1-4 heteroatoms
 selected from the group consisting of N, O, and S substituted with 0-3
 5 R³¹;

R^{12a}, at each occurrence, is independently selected from
 phenyl substituted with 0-5 R³³;
 C₃₋₁₀ carbocyclic group substituted with 0-3 R³³, and
 10 5-10 membered heterocyclic ring system containing from 1-4 heteroatoms
 selected from the group consisting of N, O, and S substituted with 0-3
 R³¹;

R¹³, at each occurrence, is independently selected from
 15 H, C₁₋₄ alkyl, C₂₋₄ alkenyl, and C₂₋₄ alkynyl;

alternatively, R¹² and R¹³ join to form a 5- or 6-membered ring optionally
 substituted with -O- or -N(R¹⁴)-;

20 alternatively, R¹² and R¹³ when attached to N may be combined to form a 9- or 10-
 membered bicyclic heterocyclic ring system containing from 1-3 heteroatoms
 selected from the group consisting of N, O, and S; wherein said bicyclic
 heterocyclic ring system is selected from indolyl, indolinyl, indazolyl,
 benzimidazolyl, benzimidazoliny, benztriazolyl, benzoxazolyl,
 25 benzoxazoliny, benzthiazolyl, and dioxobenzthiazolyl; wherein said bicyclic
 heterocyclic ring system is substituted with 0-1 R¹⁶;

R¹⁴, at each occurrence, is independently selected from H, methyl, ethyl, propyl, and
 butyl;

30

R¹⁵, at each occurrence, is independently selected from H, methyl, ethyl, propyl, and butyl;

5 R¹⁶, at each occurrence, is independently selected from
H, OH, F, Cl, CN, NO₂, methyl, ethyl, methoxy, ethoxy, trifluoromethyl, and trifluoromethoxy;

10 R³¹, at each occurrence, is independently selected from
H, OH, halo, CF₃, methyl, ethyl, and propyl;

15 R³³, at each occurrence, is independently selected from
H, OH, halo, CN, NO₂, CF₃, SO₂R⁴⁵, NR⁴⁶R⁴⁷, -C(=O)H,
C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl,
C₃₋₆ cycloalkyl, C₁₋₄ haloalkyl, C₁₋₄ haloalkyl-oxy-, C₁₋₄ alkyloxy-,
C₁₋₄ alkylthio-, C₁₋₄ alkyl-C(=O)-, C₁₋₄ alkyl-C(=O)NH-, C₁₋₄ alkyl-
OC(=O)-,
C₁₋₄ alkyl-C(=O)O-, C₃₋₆ cycloalkyl-oxy-, C₃₋₆ cycloalkylmethyl-oxy-;
C₁₋₆ alkyl substituted with OH, methoxy, ethoxy, propoxy, or butoxy; and
C₂₋₆ alkenyl substituted with OH, methoxy, ethoxy, propoxy, or butoxy;

20 R⁴¹, at each occurrence, is independently selected from
H, CF₃, halo, OH, CO₂H, SO₂R⁴⁵, NR⁴⁶R⁴⁷, NO₂, CN,
C₂₋₄ alkenyl, C₂₋₄ alkynyl, C₁₋₃ alkoxy, C₁₋₃ haloalkyl, and C₁₋₃ alkyl;

25 R⁴², at each occurrence, is independently selected from
H, CF₃, halo, OH, CO₂H, SO₂R⁴⁵, NR⁴⁶R⁴⁷, NO₂, CN, CH(=NH)NH₂,
NHC(=NH)NH₂,
C₂₋₄ alkenyl, C₂₋₄ alkynyl, C₁₋₃ alkoxy, C₁₋₃ haloalkyl, C₃₋₆ cycloalkyl, and
C₁₋₃ alkyl;

R⁴³ is cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, phenyl, or pyridyl, each substituted with 0-3 R⁴⁴;

- 5 R⁴⁴, at each occurrence, is independently selected from H, halo, -OH, NR⁴⁶R⁴⁷, CO₂H, SO₂R⁴⁵, -CF₃, -OCF₃, -CN, -NO₂, methyl, ethyl, propyl, butyl, methoxy, ethoxy, propoxy, and butoxy;

R⁴⁵ is methyl, ethyl, propyl, or butyl;

10

R⁴⁶, at each occurrence, is independently selected from H, methyl, ethyl, propyl, and butyl;

15

R⁴⁷, at each occurrence, is independently selected from H, methyl, ethyl, propyl, and butyl;

k is 1;

m is 1; and

n is 0, 1 or 2.

20

In a more preferred embodiment, the present invention provides the method as defined in Claim 2 where in the compound administered:

- 25 X is -CH₂-;

R¹ is selected from H,

C₁₋₅ alkyl substituted with 0-1 R²,

C₂₋₅ alkenyl substituted with 0-1 R², and

30

C₂₋₃ alkynyl substituted with 0-1 R²;

R² is C₃₋₆ cycloalkyl;

R⁵ is H, methyl, ethyl, or propyl;

5

R^{6a} is H, methyl, or ethyl;

R^{6b} is H;

10 R⁷ and R⁹, at each occurrence, are independently selected from
H, F, Cl, -CH₃, -OCH₃, -CF₃, -OCF₃, -CN, and -NO₂,

R⁸ is selected from

methyl substituted with R¹¹;

15 ethenyl substituted with R¹¹;

OR¹², SR¹², NR¹²R¹³, NR¹²C(O)R¹⁵, NR¹²C(O)OR¹⁵, NR¹²S(O)₂R¹⁵,
and NR¹²C(O)NHR¹⁵;

R¹¹ is selected from

20 phenyl- substituted with 0-5 fluoro;

2-(H₃CCH₂C(=O))-phenyl- substituted with R³³;

2-(H₃CC(=O))-phenyl- substituted with R³³;

2-(HC(=O))-phenyl- substituted with R³³;

2-(H₃CCH(OH))-phenyl- substituted with R³³;

25 2-(H₃CCH₂CH(OH))-phenyl- substituted with R³³;

2-(HOCH₂)-phenyl- substituted with R³³;

2-(HOCH₂CH₂)-phenyl- substituted with R³³;

2-(H₃COCH₂)-phenyl- substituted with R³³;

- 2-(H₃COCH₂CH₂)-phenyl- substituted with R³³;
 2-(H₃CCH(OMe))-phenyl- substituted with R³³;
 2-(H₃COC(=O))-phenyl- substituted with R³³;
 2-(HOCH₂CH=CH)-phenyl- substituted with R³³;
 5 2-((MeOC=O)CH=CH)-phenyl- substituted with R³³;
 2-(methyl)-phenyl- substituted with R³³;
 2-(ethyl)-phenyl- substituted with R³³;
 2-(i-propyl)-phenyl- substituted with R³³;
 2-(F₃C)-phenyl- substituted with R³³;
 10 2-(NC)-phenyl- substituted with R³³;
 2-(H₃CO)-phenyl- substituted with R³³;
 2-(fluoro)-phenyl- substituted with R³³;
 2-(chloro)-phenyl- substituted with R³³;
 3-(NC)-phenyl- substituted with R³³;
 15 3-(H₃CO)-phenyl- substituted with R³³;
 3-(fluoro)-phenyl- substituted with R³³;
 3-(chloro)-phenyl- substituted with R³³;
 4-(NC)-phenyl- substituted with R³³;
 4-(fluoro)-phenyl- substituted with R³³;
 20 4-(chloro)-phenyl- substituted with R³³;
 4-(H₃CS)-phenyl- substituted with R³³;
 4-(H₃CO)-phenyl- substituted with R³³;
 4-(ethoxy)-phenyl- substituted with R³³;
 4-(i-propoxy)-phenyl- substituted with R³³;
 25 4-(i-butoxy)-phenyl- substituted with R³³;
 4-(H₃CCH₂CH₂C(=O))-phenyl- substituted with R³³;
 4-((H₃C)₂CHC(=O))-phenyl- substituted with R³³;

- 4-(H₃CCH₂C(=O))-phenyl- substituted with R³³;
- 4-(H₃CC(=O))-phenyl- substituted with R³³;
- 4-(H₃CCH₂CH₂CH(OH))-phenyl- substituted with R³³;
- 4-((H₃C)₂CHCH(OH))-phenyl- substituted with R³³;
- 5 4-(H₃CCH₂CH(OH))-phenyl- substituted with R³³;
- 4-(H₃CCH(OH))-phenyl- substituted with R³³;
- 4-(cyclopropyloxy)-phenyl- substituted with R³³;
- 4-(cyclobutyloxy)-phenyl- substituted with R³³; and
- 4-(cyclopentyloxy)-phenyl- substituted with R³³;

10

R¹² is selected from

- phenyl- substituted with 0-5 fluoro;
- 2-(H₃CCH₂C(=O))-phenyl- substituted with R³³;
- 2-(H₃CC(=O))-phenyl- substituted with R³³;
- 15 2-(HC(=O))-phenyl- substituted with R³³;
- 2-(H₃CCH(OH))-phenyl- substituted with R³³;
- 2-(H₃CCH₂CH(OH))-phenyl- substituted with R³³;
- 2-(HOCH₂)-phenyl- substituted with R³³;
- 2-(HOCH₂CH₂)-phenyl- substituted with R³³;
- 20 2-(H₃COCH₂)-phenyl- substituted with R³³;
- 2-(H₃COCH₂CH₂)-phenyl- substituted with R³³;
- 2-(H₃CCH(OMe))-phenyl- substituted with R³³;
- 2-(H₃COC(=O))-phenyl- substituted with R³³;
- 2-(HOCH₂CH=CH)-phenyl- substituted with R³³;
- 25 2-((MeOC=O)CH=CH)-phenyl- substituted with R³³;
- 2-(methyl)-phenyl- substituted with R³³;

- 2-(ethyl)-phenyl- substituted with R³³;
- 2-(i-propyl)-phenyl- substituted with R³³;
- 2-(F₃C)-phenyl- substituted with R³³;
- 2-(NC)-phenyl- substituted with R³³;
- 5 2-(H₃CO)-phenyl- substituted with R³³;
- 2-(fluoro)-phenyl- substituted with R³³;
- 2-(chloro)-phenyl- substituted with R³³;
- 3-(NC)-phenyl- substituted with R³³;
- 3-(H₃CO)-phenyl- substituted with R³³;
- 10 3-(fluoro)-phenyl- substituted with R³³;
- 3-(chloro)-phenyl- substituted with R³³;
- 4-(NC)-phenyl- substituted with R³³;
- 4-(fluoro)-phenyl- substituted with R³³;
- 4-(chloro)-phenyl- substituted with R³³;
- 15 4-(H₃CS)-phenyl- substituted with R³³;
- 4-(H₃CO)-phenyl- substituted with R³³;
- 4-(ethoxy)-phenyl- substituted with R³³;
- 4-(i-propoxy)-phenyl- substituted with R³³;
- 4-(i-butoxy)-phenyl- substituted with R³³;
- 20 4-(H₃CCH₂CH₂C(=O))-phenyl- substituted with R³³;
- 4-((H₃C)₂CHC(=O))-phenyl- substituted with R³³;
- 4-(H₃CCH₂C(=O))-phenyl- substituted with R³³;
- 4-(H₃CC(=O))-phenyl- substituted with R³³;
- 4-(H₃CCH₂CH₂CH(OH))-phenyl- substituted with R³³;
- 25 4-((H₃C)₂CHCH(OH))-phenyl- substituted with R³³;
- 4-(H₃CCH₂CH(OH))-phenyl- substituted with R³³;
- 4-(H₃CCH(OH))-phenyl- substituted with R³³;

4-(cyclopropyloxy)-phenyl- substituted with R³³;
4-(cyclobutyloxy)-phenyl- substituted with R³³; and
4-(cyclopentyloxy)-phenyl- substituted with R³³;

5 R¹³ is H, methyl, or ethyl;

alternatively, R¹² and R¹³ join to form a 5- or 6-membered ring selected from
pyrrolyl, pyrrolidinyl, imidazolyl, piperidinyl, piperizinyl,
methylpiperizinyl, and morpholinyl;

10

alternatively, R¹² and R¹³ when attached to N may be combined to form a 9- or 10-
membered bicyclic heterocyclic ring system containing from 1-3 heteroatoms
selected from the group consisting of N, O, and S; wherein said bicyclic
heterocyclic ring system is selected from indolyl, indolinyl, indazolyl,
15 benzimidazolyl, benzimidazoliny, benztriazolyl, benzoxazolyl,
benzoxazoliny, benzthiazolyl, and dioxobenzthiazolyl; wherein said bicyclic
heterocyclic ring system is substituted with 0-1 R¹⁶;

R¹⁵ is H, methyl, ethyl, propyl, or butyl;

20

R¹⁶, at each occurrence, is independently selected from
H, OH, F, Cl, CN, NO₂, methyl, ethyl, methoxy, ethoxy, trifluoromethyl, and
trifluoromethoxy;

25 R³³, at each occurrence, is independently selected from
H, F, Cl, -CH₃, -OCH₃, -CF₃, -OCF₃, -CN, and -NO₂;

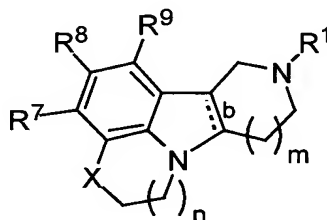
k is 1;

m is 1; and

30 n is 1 or 2.

In a more preferred embodiment, the present invention provides the method as defined in Claim 2 where the compound administered is a compound of Formula (I-a):

5



(I-a)

wherein:

10

b is a single bond;

X is -CH₂-, -CH(OH)-, or -C(=O)-;

15 R¹ is selected from

hydrogen, methyl, ethyl, n-propyl, n-butyl, s-butyl,
t-butyl, n-pentyl, n-hexyl, 2-propyl, 2-butyl, 2-pentyl, 2-hexyl, 2-methylpropyl,
2-methylbutyl, 2-methylpentyl, 2-ethylbutyl, 3-methylpentyl, 3-
methylbutyl,

20

4-methylpentyl, 2-fluoroethyl, 2,2-difluoroethyl,
2,2,2-trifluoroethyl,

25

2-propenyl, 2-methyl-2-propenyl, trans-2-butenyl,
3-methyl-butenyl, 3-butenyl, trans-2-pentenyl,
cis-2-pentenyl, 4-pentenyl, 4-methyl-3-pentenyl,
3,3-dichloro-2-propenyl, trans-3-phenyl-2-propenyl,

- cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cyclopropylmethyl,
cyclobutylmethyl, cyclopentylmethyl, cyclohexylmethyl,
- benzyl, 2-methylbenzyl, 3-methylbenzyl, 4-methylbenzyl, 2,5-dimethylbenzyl,
2,4-dimethylbenzyl, 3,5-dimethylbenzyl,
2,4,6-trimethyl-benzyl, 3-methoxy-benzyl, 3,5-dimethoxy-benzyl,
pentafluorobenzyl, 2-phenylethyl, 1-phenyl-2-propyl, 4-phenylbutyl, 4-phenylbenzyl, 2-phenylbenzyl,
- (2,3-dimethoxy-phenyl)C(=O)-, (2,5-dimethoxy-phenyl)C(=O)-, (3,4-dimethoxy-phenyl)C(=O)-,
(3,5-dimethoxy-phenyl)C(=O)-, cyclopropyl-C(=O)-,
isopropyl-C(=O)-, ethyl-CO₂-, propyl-CO₂-, t-butyl-CO₂-,
2,6-dimethoxy-benzyl, 2,4-dimethoxy-benzyl,
2,4,6-trimethoxy-benzyl, 2,3-dimethoxy-benzyl,
2,4,5-trimethoxy-benzyl, 2,3,4-trimethoxy-benzyl,
3,4-dimethoxy-benzyl, 3,4,5-trimethoxy-benzyl,
(4-fluoro-phenyl)ethyl,
- CH=CH₂, -CH₂-CH=CH₂, -CH=CH-CH₃, -C≡CH, -C≡C-CH₃, and
-CH₂-C≡CH;
- R⁷, R⁸, and R⁹, at each occurrence, are independently selected from
hydrogen, fluoro, chloro, bromo, cyano, methyl, ethyl, propyl, isopropyl, butyl,
t-butyl, nitro, trifluoromethyl, methoxy, ethoxy, isopropoxy,
trifluoromethoxy, phenyl,
methylC(=O)-, ethylC(=O)-, propylC(=O)-, isopropylC(=O)-, butylC(=O)-,
phenylC(=O)-,

- methylCO₂-, ethylCO₂-, propylCO₂-, isopropylCO₂-, butylCO₂-,
phenylCO₂-,
- 5 dimethylamino-S(=O)-, diethylamino-S(=O)-,
dipropylamino-S(=O)-, di-isopropylamino-S(=O)-, dibutylamino-S(=O)-,
diphenylamino-S(=O)-,
- 10 dimethylamino-SO₂-, diethylamino-SO₂-, dipropylamino-SO₂-, di-
isopropylamino-SO₂-, dibutylamino-SO₂-,
diphenylamino-SO₂-,
- 15 dimethylamino-C(=O)-, diethylamino-C(=O)-,
dipropylamino-C(=O)-, di-isopropylamino-C(=O)-, dibutylamino-C(=O)-,
diphenylamino-C(=O)-,
- 20 2-chlorophenyl, 2-fluorophenyl, 2-bromophenyl, 2-cyanophenyl, 2-
methylphenyl, 2-trifluoromethylphenyl,
2-methoxyphenyl, 2-trifluoromethoxyphenyl,
- 25 3-chlorophenyl, 3-fluorophenyl, 3-bromophenyl,
3-cyanophenyl, 3-methylphenyl, 3-ethylphenyl,
3-propylphenyl, 3-isopropylphenyl, 3-butylphenyl,
3-trifluoromethylphenyl, 3-methoxyphenyl,
3-isopropoxyphenyl, 3-trifluoromethoxyphenyl,
- 30 4-chlorophenyl, 4-fluorophenyl, 4-bromophenyl,
4-cyanophenyl, 4-methylphenyl, 4-ethylphenyl,
4-propylphenyl, 4-isopropylphenyl, 4-butylphenyl,
4-trifluoromethylphenyl, 4-methoxyphenyl,
4-isopropoxyphenyl, 4-trifluoromethoxyphenyl,

- 4-thiomethoxyphenyl,
- 2,3-dichlorophenyl, 2,3-difluorophenyl, 2,3-dimethylphenyl,
2,3-ditrifluoromethylphenyl, 2,3-dimethoxyphenyl,
5 2,3-ditrifluoromethoxyphenyl,
- 2,4-dichlorophenyl, 2,4-difluorophenyl, 2,4-dimethylphenyl,
2,4-ditrifluoromethylphenyl, 2,4-dimethoxyphenyl,
2,4-ditrifluoromethoxyphenyl,
10
- 2,5-dichlorophenyl, 2,5-difluorophenyl, 2,5-dimethylphenyl,
2,5-ditrifluoromethylphenyl, 2,5-dimethoxyphenyl,
2,5-ditrifluoromethoxyphenyl,
- 15 2,6-dichlorophenyl, 2,6-difluorophenyl, 2,6-dimethylphenyl,
2,6-ditrifluoromethylphenyl, 2,6-dimethoxyphenyl,
2,6-ditrifluoromethoxyphenyl,
- 3,4-dichlorophenyl, 3,4-difluorophenyl, 3,4-dimethylphenyl,
20 3,4-ditrifluoromethylphenyl, 3,4-dimethoxyphenyl,
3,4-ditrifluoromethoxyphenyl,
- 2,4,6-trichlorophenyl, 2,4,6-trifluorophenyl,
2,4,6-trimethylphenyl, 2,4,6-tritrifluoromethylphenyl,
25 2,4,6-trimethoxyphenyl, 2,4,6-tritrifluoromethoxyphenyl,
- 2-chloro-4-CF₃-phenyl, 2-fluoro-3-chloro-phenyl,
2-chloro-4-CF₃-phenyl, 2-chloro-4-methoxy-phenyl,
2-methoxy-4-isopropyl-phenyl, 2-CF₃-4-methoxy-phenyl,
30 2-methyl-4-methoxy-5-fluoro-phenyl,
2-methyl-4-methoxy-phenyl, 2-chloro-4-CF₃O-phenyl,

- 2,4,5-trimethyl-phenyl, 2-methyl-4-chloro-phenyl,
- methyl-C(=O)NH-, ethyl-C(=O)NH-, propyl-C(=O)NH-,
isopropyl-C(=O)NH-, butyl-C(=O)NH-, phenyl-C(=O)NH-,
- 5 4-acetylphenyl, 3-acetamidophenyl, 4-pyridyl, 2-furanyl,
2-thiophenyl, 2-naphthyl;
- 10 2-Me-5-F-phenyl, 2-F-5-Me-phenyl, 2-MeO-5-F-phenyl,
2-Me-3-Cl-phenyl, 3-NO₂-phenyl, 2-NO₂-phenyl,
2-Cl-3-Me-phenyl, 2-Me-4-EtO-phenyl, 2-Me-4-F-phenyl,
2-Cl-6-F-phenyl, 2-Cl-4-(CHF₂)O-phenyl,
2,4-diMeO-6-F-phenyl, 2-CF₃-6-F-phenyl,
2-MeS-phenyl, 2,6-diCl-4-MeO-phenyl,
- 15 2,3,4-triF-phenyl, 2,6-diF-4-Cl-phenyl,
2,3,4,6-tetraF-phenyl, 2,3,4,5,6-pentaF-phenyl,
2-CF₃-4-EtO-phenyl, 2-CF₃-4-iPrO-phenyl,
2-CF₃-4-Cl-phenyl, 2-CF₃-4-F-phenyl, 2-Cl-4-EtO-phenyl,
2-Cl-4-iPrO-phenyl, 2-Et-4-MeO-phenyl,
- 20 2-CHO-4-MeO-phenyl, 2-CH(OH)Me-4-MeO-phenyl,
2-CH(OMe)Me-4-MeO-phenyl, 2-C(=O)Me-4-MeO-phenyl,
2-CH₂(OH)-4-MeO-phenyl, 2-CH₂(OMe)-4-MeO-phenyl,
2-CH(OH)Et-4-MeO-phenyl, 2-C(=O)Et-4-MeO-phenyl,
(Z)-2-CH=CHCO₂Me-4-MeO-phenyl,
- 25 2-CH₂CH₂CO₂Me-4-MeO-phenyl,
(Z)-2-CH=CHCH₂(OH)-4-MeO-phenyl,
(E)-2-CH=CHCO₂Me-4-MeO-phenyl,
(E)-2-CH=CHCH₂(OH)-4-MeO-phenyl,
2-CH₂CH₂OMe-4-MeO-phenyl,
- 30 2-F-4-MeO-phenyl, 2-Cl-4-F-phenyl,

(2-Cl-phenyl)-CH=CH-, (3-Cl-phenyl)-CH=CH-,
 (2,6-diF-phenyl)-CH=CH-, -CH₂CH=CH₂,
 phenyl-CH=CH-, (2-Me-4-MeO-phenyl)-CH=CH-,
 cyclohexyl, cyclopentyl, cyclohexylmethyl,
 5 -CH₂CH₂CO₂Et, -(CH₂)₃CO₂Et, -(CH₂)₄CO₂Et,
 benzyl, 2-F-benzyl, 3-F-benzyl, 4-F-benzyl,
 3-MeO-benzyl, 3-OH-benzyl, 2-MeO-benzyl,
 2-OH-benzyl, 2-CO₂Me-3-MeO-phenyl,
 2-Me-4-CN-phenyl, 2-Me-3-CN-phenyl, 2-CF₃-4-CN-phenyl,
 10 3-CHO-phenyl, 3-CH₂(OH)-phenyl, 3-CH₂(OMe)-phenyl,
 3-CH₂(NMe₂)-phenyl, 3-CN-4-F-phenyl,
 3-CONH₂-4-F-phenyl, 2-CH₂(NH₂)-4-MeO-phenyl-,
 phenyl-NH-, (4-F-phenyl)-NH-, (2,4-diCl-phenyl)-NH-,
 phenyl-C(=O)NH-, benzyl-NH-, (2-Me-4-MeO-phenyl)-NH-,
 15 (2-F-4-MeO-phenyl)-NH-, (2-Me-4-F-phenyl)-NH-,
 phenyl-S-, -NMe₂, 1-pyrrolidinyl, and
 -N(tosylate)₂,

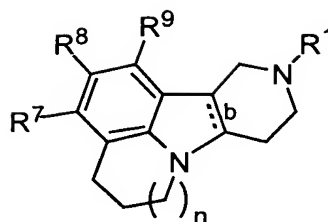
provided that two of R⁷, R⁸, and R⁹, are independently selected from hydrogen,
 20 fluoro, chloro, bromo, cyano, methyl, ethyl, propyl, isopropyl, butyl, t-butyl,
 nitro, trifluoromethyl, methoxy, ethoxy, isopropoxy, and trifluoromethoxy;

m is 1; and

n is 0, 1 or 2.

25

In a more preferred embodiment, the present invention provides the method as
 defined in Claim 7 where the compound administered is a compound of Formula (V):



(V)

wherein:

5

b is a single bond, wherein the bridge hydrogens are in a cis position;

R¹ is selected from

- hydrogen, methyl, ethyl, n-propyl, n-butyl, s-butyl,
 10 t-butyl, n-pentyl, n-hexyl, 2-propyl, 2-butyl, 2-pentyl, 2-hexyl, 2-methylpropyl,
 2-methylbutyl, 2-methylpentyl, 2-ethylbutyl, 3-methylpentyl, 3-
 methylbutyl,
 4-methylpentyl, 2-fluoroethyl, 2,2-difluoroethyl,
 2,2,2-trifluoroethyl, 2-propenyl, 2-methyl-2-propenyl, trans-2-butenyl, 3-
 15 methyl-butenyl, 3-butenyl,
 trans-2-pentenyl, cis-2-pentenyl, 4-pentenyl,
 4-methyl-3-pentenyl, 3,3-dichloro-2-propenyl,
 trans-3-phenyl-2-propenyl, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl,
 cyclopropylmethyl, cyclobutylmethyl, cyclopentylmethyl,
 20 cyclohexylmethyl,
 -CH=CH₂, -CH₂-CH=CH₂, -CH=CH-CH₃, -C≡CH, -C≡C-CH₃,
 and -CH₂-C≡CH;

R⁷ and R⁹, at each occurrence, are independently selected from hydrogen, fluoro,
 25 methyl, trifluoromethyl, and methoxy;

R⁸ is selected from

- hydrogen, fluoro, chloro, bromo, cyano, methyl, ethyl, propyl, isopropyl, butyl,
t-butyl, nitro, trifluoromethyl, methoxy, ethoxy, isopropoxy,
trifluoromethoxy, phenyl,
- 5 methylC(=O)-, ethylC(=O)-, propylC(=O)-, isopropylC(=O)-, butylC(=O)-,
phenylC(=O)-,
- methylCO₂-, ethylCO₂-, propylCO₂-, isopropylCO₂-, butylCO₂-,
phenylCO₂-,
- 10 dimethylamino-S(=O)-, diethylamino-S(=O)-,
dipropylamino-S(=O)-, di-isopropylamino-S(=O)-, dibutylamino-S(=O)-,
diphenylamino-S(=O)-,
- 15 dimethylamino-SO₂-, diethylamino-SO₂-, dipropylamino-SO₂-, di-
isopropylamino-SO₂-, dibutylamino-SO₂-,
diphenylamino-SO₂-,
- 20 dimethylamino-C(=O)-, diethylamino-C(=O)-,
dipropylamino-C(=O)-, di-isopropylamino-C(=O)-, dibutylamino-C(=O)-,
diphenylamino-C(=O)-,
- 2-chlorophenyl, 2-fluorophenyl, 2-bromophenyl, 2-cyanophenyl, 2-
methylphenyl, 2-trifluoromethylphenyl,
- 25 2-methoxyphenyl, 2-trifluoromethoxyphenyl,
- 3-chlorophenyl, 3-fluorophenyl, 3-bromophenyl,
3-cyanophenyl, 3-methylphenyl, 3-ethylphenyl,
3-propylphenyl, 3-isopropylphenyl, 3-butylphenyl,
- 30 3-trifluoromethylphenyl, 3-methoxyphenyl,
3-isopropoxyphenyl, 3-trifluoromethoxyphenyl,

- 3-thiomethoxyphenyl,
- 4-chlorophenyl, 4-fluorophenyl, 4-bromophenyl,
 4-cyanophenyl, 4-methylphenyl, 4-ethylphenyl,
 5 4-propylphenyl, 4-isopropylphenyl, 4-butylphenyl,
 4-trifluoromethylphenyl, 4-methoxyphenyl,
 4-isopropoxyphenyl, 4-trifluoromethoxyphenyl,
 4-thiomethoxyphenyl,
- 10 2,3-dichlorophenyl, 2,3-difluorophenyl, 2,3-dimethylphenyl,
 2,3-ditrifluoromethylphenyl, 2,3-dimethoxyphenyl,
 2,3-ditrifluoromethoxyphenyl,
- 15 2,4-dichlorophenyl, 2,4-difluorophenyl, 2,4-dimethylphenyl,
 2,4-ditrifluoromethylphenyl, 2,4-dimethoxyphenyl,
 2,4-ditrifluoromethoxyphenyl,
- 20 2,5-dichlorophenyl, 2,5-difluorophenyl, 2,5-dimethylphenyl,
 2,5-ditrifluoromethylphenyl, 2,5-dimethoxyphenyl,
 2,5-ditrifluoromethoxyphenyl,
- 25 2,6-dichlorophenyl, 2,6-difluorophenyl, 2,6-dimethylphenyl,
 2,6-ditrifluoromethylphenyl, 2,6-dimethoxyphenyl,
 2,6-ditrifluoromethoxyphenyl,
- 30 3,4-dichlorophenyl, 3,4-difluorophenyl, 3,4-dimethylphenyl,
 3,4-ditrifluoromethylphenyl, 3,4-dimethoxyphenyl,
 3,4-ditrifluoromethoxyphenyl,
- 2,4,6-trichlorophenyl, 2,4,6-trifluorophenyl,
 2,4,6-trimethylphenyl, 2,4,6-tritrifluoromethylphenyl,
 2,4,6-trimethoxyphenyl, 2,4,6-tritrifluoromethoxyphenyl,

- 2-chloro-4-CF₃-phenyl, 2-fluoro-3-chloro-phenyl,
 2-chloro-4-CF₃-phenyl, 2-chloro-4-methoxy-phenyl,
 2-methoxy-4-isopropyl-phenyl, 2-CF₃-4-methoxy-phenyl,
 5 2-methyl-4-methoxy-5-fluoro-phenyl,
 2-methyl-4-methoxy-phenyl, 2-chloro-4-CF₃O-phenyl,
 2,4,5-trimethyl-phenyl, 2-methyl-4-chloro-phenyl,
- 10 methyl-C(=O)NH-, ethyl-C(=O)NH-, propyl-C(=O)NH-,
 isopropyl-C(=O)NH-, butyl-C(=O)NH-, phenyl-C(=O)NH-,
- 4-acetylphenyl, 3-acetamidophenyl, 4-pyridyl, 2-furanyl,
 2-thiophenyl, 2-naphthyl;
- 15 2-Me-5-F-phenyl, 2-F-5-Me-phenyl, 2-MeO-5-F-phenyl,
 2-Me-3-Cl-phenyl, 3-NO₂-phenyl, 2-NO₂-phenyl,
 2-Cl-3-Me-phenyl, 2-Me-4-EtO-phenyl, 2-Me-4-F-phenyl,
 2-Cl-6-F-phenyl, 2-Cl-4-(CHF₂)O-phenyl,
 2,4-diMeO-6-F-phenyl, 2-CF₃-6-F-phenyl,
 20 2-MeS-phenyl, 2,6-diCl-4-MeO-phenyl,
 2,3,4-triF-phenyl, 2,6-diF-4-Cl-phenyl,
 2,3,4,6-tetraF-phenyl, 2,3,4,5,6-pentaF-phenyl,
 2-CF₃-4-EtO-phenyl, 2-CF₃-4-iPrO-phenyl,
 2-CF₃-4-Cl-phenyl, 2-CF₃-4-F-phenyl, 2-Cl-4-EtO-phenyl,
 25 2-Cl-4-iPrO-phenyl, 2-Et-4-MeO-phenyl,
 2-CHO-4-MeO-phenyl, 2-CH(OH)Me-4-MeO-phenyl,
 2-CH(OMe)Me-4-MeO-phenyl, 2-C(=O)Me-4-MeO-phenyl,
 2-CH₂(OH)-4-MeO-phenyl, 2-CH₂(OMe)-4-MeO-phenyl,
 2-CH(OH)Et-4-MeO-phenyl, 2-C(=O)Et-4-MeO-phenyl,
 30 (Z)-2-CH=CHCO₂Me-4-MeO-phenyl,

- 2-CH₂CH₂CO₂Me-4-MeO-phenyl,
 (Z)-2-CH=CHCH₂(OH)-4-MeO-phenyl,
 (E)-2-CH=CHCO₂Me-4-MeO-phenyl,
 (E)-2-CH=CHCH₂(OH)-4-MeO-phenyl,
 5 2-CH₂CH₂OMe-4-MeO-phenyl,
 2-F-4-MeO-phenyl, 2-Cl-4-F-phenyl,
 (2-Cl-phenyl)-CH=CH-, (3-Cl-phenyl)-CH=CH-,
 (2,6-diF-phenyl)-CH=CH-, -CH₂CH=CH₂,
 phenyl-CH=CH-, (2-Me-4-MeO-phenyl)-CH=CH-,
 10 cyclohexyl, cyclopentyl, cyclohexylmethyl,
 -CH₂CH₂CO₂Et, -(CH₂)₃CO₂Et, -(CH₂)₄CO₂Et,
 benzyl, 2-F-benzyl, 3-F-benzyl, 4-F-benzyl,
 3-MeO-benzyl, 3-OH-benzyl, 2-MeO-benzyl,
 2-OH-benzyl, 2-CO₂Me-3-MeO-phenyl,
 15 2-Me-4-CN-phenyl, 2-Me-3-CN-phenyl, 2-CF₃-4-CN-phenyl,
 3-CHO-phenyl, 3-CH₂(OH)-phenyl, 3-CH₂(OMe)-phenyl,
 3-CH₂(NMe₂)-phenyl, 3-CN-4-F-phenyl,
 3-CONH₂-4-F-phenyl, 2-CH₂(NH₂)-4-MeO-phenyl-,
 phenyl-NH-, (4-F-phenyl)-NH-, (2,4-diCl-phenyl)-NH-,
 20 phenyl-C(=O)NH-, benzyl-NH-, (2-Me-4-MeO-phenyl)-NH-,
 (2-F-4-MeO-phenyl)-NH-, (2-Me-4-F-phenyl)-NH-,
 phenyl-S-, -NMe₂, 1-pyrrolidinyl, and
 -N(tosylate)₂; and
 25 n is 0, 1 or 2.

In a more preferred embodiment, the present invention provides the method as defined in Claim 1 where in the compound administered:

30

X is -CHR¹⁰- or -C(=O)-;

R¹ is selected from

- C₁₋₆ alkyl substituted with Z,
- 5 C₂₋₆ alkenyl substituted with Z,
- C₂₋₆ alkynyl substituted with Z,
- C₃₋₆ cycloalkyl substituted with Z,
- aryl substituted with Z,
- 5-6 membered heterocyclic ring system containing at least one heteroatom
- 10 selected from the group consisting of N, O, and S, said heterocyclic ring system substituted with Z;
- C₁₋₆ alkyl substituted with 0-2 R²,
- C₂₋₆ alkenyl substituted with 0-2 R²,
- C₂₋₆ alkynyl substituted with 0-2 R²,
- 15 aryl substituted with 0-2 R², and
- 5-6 membered heterocyclic ring system containing at least one heteroatom
- selected from the group consisting of N, O, and S, said heterocyclic ring system substituted with 0-2 R²;

20 Z is selected from H,

- CH(OH)R²,
- C(ethylenedioxy)R²,
- OR²,
- SR²,
- 25 -NR²R³,
- C(O)R²,
- C(O)NR²R³,
- NR³C(O)R²,
- C(O)OR²,

-OC(O)R²,
 -CH(=NR⁴)NR²R³,
 -NHC(=NR⁴)NR²R³,
 -S(O)R²,
 5 -S(O)₂R²,
 -S(O)₂NR²R³, and -NR³S(O)₂R²;

R², at each occurrence, is independently selected from

10 C₁₋₄ alkyl,
 C₂₋₄ alkenyl,
 C₂₋₄ alkynyl,
 C₃₋₆ cycloalkyl,
 aryl substituted with 0-5 R⁴²,
 C₃₋₁₀ carbocyclic group substituted with 0-3 R⁴¹, and
 15 5-10 membered heterocyclic ring system containing from 1-4 heteroatoms
 selected from the group consisting of N, O, and S substituted with 0-3
 R⁴¹;

R³, at each occurrence, is independently selected from

20 H, C₁₋₄ alkyl, C₂₋₄ alkenyl, C₂₋₄ alkynyl, and
 C₁₋₄ alkoxy;

alternatively, R² and R³ join to form a 5- or 6-membered ring optionally substituted
 with -O- or -N(R⁴)-;

25

R⁴, at each occurrence, is independently selected from H, methyl, ethyl, propyl, and
 butyl;

R⁵ is H, methyl, ethyl, propyl, or butyl;

R^{6a} is selected from

H, -OH, -NR⁴⁶R⁴⁷, -CF₃,

C₁₋₄ alkyl, C₂₋₄ alkenyl, C₂₋₄ alkynyl, C₁₋₄ alkoxy, C₁₋₄ haloalkyl, C₃₋₆

5 cycloalkyl, and

aryl substituted with 0-3 R⁴⁴;

R^{6b} is H;

10 R⁷, R⁸, and R⁹, at each occurrence, are independently selected from

H, halo, -CF₃, -OCF₃, -OH, -CN, -NO₂, -NR⁴⁶R⁴⁷,

C₁₋₈ alkyl, C₂₋₈ alkenyl, C₂₋₈ alkynyl, C₁₋₄ haloalkyl, C₁₋₈ alkoxy, (C₁₋₄
haloalkyl)oxy,

C₁₋₄ alkyl substituted with 0-2 R¹¹,

15 C₃₋₁₀ carbocyclic group substituted with 0-3 R³³,

aryl substituted with 0-5 R³³,

5-10 membered heterocyclic ring system containing from 1-4 heteroatoms

selected from the group consisting of N, O, and S substituted with 0-3

R³¹;

20

OR¹², SR¹², NR¹²R¹³, C(O)H, C(O)R¹², C(O)NR¹²R¹³, NR¹⁴C(O)R¹²,

C(O)OR¹², OC(O)R¹², OC(O)OR¹², CH(=NR¹⁴)NR¹²R¹³,

NHC(=NR¹⁴)NR¹²R¹³, S(O)R¹², S(O)₂R¹², S(O)NR¹²R¹³,

S(O)₂NR¹²R¹³, NR¹⁴S(O)R¹², NR¹⁴S(O)₂R¹², NR¹²C(O)R¹⁵,

25 NR¹²C(O)OR¹⁵, NR¹²S(O)₂R¹⁵, and NR¹²C(O)NHR¹⁵;

R¹⁰ is selected from H, -OH,

C₁₋₆ alkyl substituted with 0-1 R^{10B},

C₂₋₆ alkenyl substituted with 0-1 R^{10B},
 C₂₋₆ alkynyl substituted with 0-1 R^{10B}, and
 C₁₋₆ alkoxy;

5 R^{10B} is selected from

C₁₋₄ alkoxy,
 C₃₋₆ cycloalkyl,
 C₃₋₁₀ carbocyclic group substituted with 0-3 R³³,
 phenyl substituted with 0-3 R³³, and

10 5-6 membered heterocyclic ring system containing 1, 2, or 3 heteroatoms
 selected from the group consisting of N, O, and S substituted with 0-2
 R⁴⁴;

R¹¹ is selected from

15 H, halo, -CF₃, -CN, -NO₂,
 C₁₋₈ alkyl, C₂₋₈ alkenyl, C₂₋₈ alkynyl, C₁₋₄ haloalkyl, C₁₋₈ alkoxy, C₃₋₁₀
 cycloalkyl,
 C₃₋₁₀ carbocyclic group substituted with 0-3 R³³,
 aryl substituted with 0-5 R³³,
 20 5-10 membered heterocyclic ring system containing from 1-4 heteroatoms
 selected from the group consisting of N, O, and S substituted with 0-3
 R³¹;

25 OR¹², SR¹², NR¹²R¹³, C(O)H, C(O)R¹², C(O)NR¹²R¹³, NR¹⁴C(O)R¹²,
 C(O)OR¹², OC(O)R¹², OC(O)OR¹², CH(=NR¹⁴)NR¹²R¹³,
 NHC(=NR¹⁴)NR¹²R¹³, S(O)R¹², S(O)₂R¹², S(O)NR¹²R¹³,
 S(O)₂NR¹²R¹³, NR¹⁴S(O)R¹², and NR¹⁴S(O)₂R¹²;

R¹², at each occurrence, is independently selected from

C₁₋₄ alkyl,

C₂₋₄ alkenyl,

C₂₋₄ alkynyl,

5 C₃₋₆ cycloalkyl,

phenyl substituted with 0-5 R³³;

C₃₋₁₀ carbocyclic group substituted with 0-3 R³³, and

5-10 membered heterocyclic ring system containing from 1-4 heteroatoms

selected from the group consisting of N, O, and S substituted with 0-3

10 R³¹;

R¹³, at each occurrence, is independently selected from

H, C₁₋₄ alkyl, C₂₋₄ alkenyl, and C₂₋₄ alkynyl;

15 alternatively, R¹² and R¹³ join to form a 5- or 6-membered ring optionally
substituted with -O- or -N(R¹⁴)-;

R¹⁴, at each occurrence, is independently selected from H and C₁₋₄ alkyl;

20 R³¹, at each occurrence, is independently selected from

H, OH, halo, CF₃, SO₂R⁴⁵, NR⁴⁶R⁴⁷, methyl, ethyl, and propyl;

R³³, at each occurrence, is independently selected from

H, OH, halo, CN, NO₂, CF₃, SO₂R⁴⁵, NR⁴⁶R⁴⁷,

25 C₁₋₃ alkyl, C₂₋₃ alkenyl, C₂₋₃ alkynyl, C₃₋₅ cycloalkyl, C₁₋₃ haloalkyl, C₁₋₃
haloalkyl-oxy-, C₁₋₃ alkyloxy-, C₁₋₃ alkylthio-, C₁₋₃ alkyl-C(=O)-,
and C₁₋₃ alkyl-C(=O)NH-;

R⁴¹, at each occurrence, is independently selected from

H, CF₃, halo, OH, CO₂H, SO₂R⁴⁵, NR⁴⁶R⁴⁷, NO₂, CN, =O,
C₂₋₈ alkenyl, C₂₋₈ alkynyl, C₁₋₄ alkoxy, C₁₋₄ haloalkyl
C₁₋₄ alkyl substituted with 0-1 R⁴³,
aryl substituted with 0-3 R⁴², and
5 5-10 membered heterocyclic ring system containing from 1-4 heteroatoms
selected from the group consisting of N, O, and S substituted with 0-3
R⁴⁴;

R⁴², at each occurrence, is independently selected from
10 H, CF₃, halo, OH, CO₂H, SO₂R⁴⁵, SR⁴⁵, NR⁴⁶R⁴⁷, OR⁴⁸, NO₂, CN,
CH(=NH)NH₂, NHC(=NH)NH₂,
C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₁₋₄ alkoxy, C₁₋₄ haloalkyl, C₃₋₆ cycloalkyl,
C₁₋₄ alkyl substituted with 0-1 R⁴³,
aryl substituted with 0-3 R⁴⁴, and
15 5-10 membered heterocyclic ring system containing from 1-4 heteroatoms
selected from the group consisting of N, O, and S substituted with 0-3
R⁴⁴;

R⁴³ is C₃₋₆ cycloalkyl or aryl substituted with 0-3 R⁴⁴;
20

R⁴⁴, at each occurrence, is independently selected from H, halo, -OH, NR⁴⁶R⁴⁷,
CO₂H, SO₂R⁴⁵, -CF₃, -OCF₃, -CN, -NO₂, C₁₋₄ alkyl, and C₁₋₄ alkoxy;

R⁴⁵ is C₁₋₄ alkyl;
25

R⁴⁶, at each occurrence, is independently selected from H and C₁₋₄ alkyl;

R⁴⁷, at each occurrence, is independently selected from H, C₁₋₄ alkyl,
-C(=O)NH(C₁₋₄ alkyl), -SO₂(C₁₋₄ alkyl),
-SO₂(phenyl), -C(=O)O(C₁₋₄ alkyl), -C(=O)(C₁₋₄ alkyl), and -C(=O)H;

5 R⁴⁸, at each occurrence, is independently selected from H, C₁₋₄ alkyl,
-C(=O)NH(C₁₋₄ alkyl), -C(=O)O(C₁₋₄ alkyl),
-C(=O)(C₁₋₄ alkyl), and -C(=O)H;

k is 1 or 2;

10 m is 0, 1, or 2; and
n is 0, 1 or 2.

In a more preferred embodiment, the present invention provides the method as
15 defined in Claim 9 where in the compound administered:

X is -CHR¹⁰- or -C(=O)-;

R¹ is selected from

20 C₂₋₅ alkyl substituted with Z,
C₂₋₅ alkenyl substituted with Z,
C₂₋₅ alkynyl substituted with Z,
C₃₋₆ cycloalkyl substituted with Z,
aryl substituted with Z,
25 5-6 membered heterocyclic ring system containing at least one heteroatom
selected from the group consisting of N, O, and S, said heterocyclic
ring system substituted with Z;
C₁₋₅ alkyl substituted with 0-2 R²,
C₂₋₅ alkenyl substituted with 0-2 R², and

C₂₋₅ alkynyl substituted with 0-2 R²;

Z is selected from H,

- CH(OH)R²,
- 5 -C(ethylenedioxy)R²,
- OR²,
- SR²,
- NR²R³,
- C(O)R²,
- 10 -C(O)NR²R³,
- NR³C(O)R²,
- C(O)OR²,
- OC(O)R²,
- CH(=NR⁴)NR²R³,
- 15 -NHC(=NR⁴)NR²R³,
- S(O)R²,
- S(O)₂R²,
- S(O)₂NR²R³, and -NR³S(O)₂R²;

20 R², at each occurrence, is independently selected from

- C₁₋₄ alkyl,
- C₂₋₄ alkenyl,
- C₂₋₄ alkynyl,
- C₃₋₆ cycloalkyl,
- 25 aryl substituted with 0-5 R⁴²;
- C₃₋₁₀ carbocyclic group substituted with 0-3 R⁴¹, and

5-10 membered heterocyclic ring system containing from 1-4 heteroatoms
selected from the group consisting of N, O, and S substituted with 0-3
R⁴¹;

- 5 R³, at each occurrence, is independently selected from
H, C₁₋₄ alkyl, C₂₋₄ alkenyl, C₂₋₄ alkynyl, and
C₁₋₄ alkoxy;

alternatively, R² and R³ join to form a 5- or 6-membered ring optionally substituted
10 with -O- or -N(R⁴)-;

R⁴, at each occurrence, is independently selected from H, methyl, ethyl, propyl, and
butyl;

- 15 R⁵ is H, methyl, or ethyl;

R^{6a} is selected from

- H, -OH, -NR⁴⁶R⁴⁷, -CF₃,
C₁₋₄ alkyl, C₂₋₄ alkenyl, C₂₋₄ alkynyl, C₁₋₄ alkoxy, C₁₋₄ haloalkyl, and C₃₋₆
20 cycloalkyl;

R^{6b} is H;

- R⁷, R⁸, and R⁹, at each occurrence, are independently selected from
25 H, halo, -CF₃, -OCF₃, -OH, -OCH₃, -CN, -NO₂, -NR⁴⁶R⁴⁷,
C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₁₋₄ haloalkyl, C₁₋₆ alkoxy, (C₁₋₄
haloalkyl)oxy,
C₁₋₄ alkyl substituted with 0-2 R¹¹,
C₃₋₁₀ carbocyclic group substituted with 0-3 R³³,

aryl substituted with 0-5 R³³,
 5-10 membered heterocyclic ring system containing from 1-4 heteroatoms
 selected from the group consisting of N, O, and S substituted with 0-3
 R³¹;

5

OR¹², SR¹², NR¹²R¹³, C(O)H, C(O)R¹², C(O)NR¹²R¹³, NR¹⁴C(O)R¹²,
 C(O)OR¹², OC(O)R¹², CH(=NR¹⁴)NR¹²R¹³, NHC(=NR¹⁴)NR¹²R¹³,
 S(O)R¹², S(O)₂R¹², S(O)₂NR¹²R¹³, NR¹⁴S(O)₂R¹², NR¹⁴S(O)R¹²,
 NR¹⁴S(O)₂R¹², NR¹²C(O)R¹⁵, NR¹²C(O)OR¹⁵, NR¹²S(O)₂R¹⁵, and
 10 NR¹²C(O)NHR¹⁵;

R¹⁰ is selected from H, -OH, C₁₋₆ alkyl, C₁₋₄ alkoxy, and
 C₁₋₂ alkyl substituted with 0-1 R^{10B};

15 R^{10B} is C₃₋₆ cycloalkyl or
 phenyl substituted with 0-3 R³³;

R¹¹ is selected from

H, halo, -CF₃, -OCF₃, -OH, -OCH₃, -CN, -NO₂, -NR⁴⁶R⁴⁷,
 20 C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₁₋₄ haloalkyl, C₁₋₆ alkoxy, (C₁₋₄
 haloalkyl)oxy,
 C₃₋₁₀ carbocyclic group substituted with 0-3 R³³,
 aryl substituted with 0-5 R³³,
 5-10 membered heterocyclic ring system containing from 1-4 heteroatoms
 25 selected from the group consisting of N, O, and S substituted with 0-3
 R³¹;

OR¹², SR¹², NR¹²R¹³, C(O)H, C(O)R¹², C(O)NR¹²R¹³, NR¹⁴C(O)R¹²,
C(O)OR¹², OC(O)R¹², CH(=NR¹⁴)NR¹²R¹³, NHC(=NR¹⁴)NR¹²R¹³,
S(O)R¹², S(O)₂R¹², S(O)₂NR¹²R¹³, and NR¹⁴S(O)₂R¹²;

5 R¹², at each occurrence, is independently selected from

C₁₋₄ alkyl,

C₂₋₄ alkenyl,

C₂₋₄ alkynyl,

C₃₋₆ cycloalkyl,

10 phenyl substituted with 0-5 R³³;

C₃₋₁₀ carbocyclic group substituted with 0-3 R³³, and

5-10 membered heterocyclic ring system containing from 1-4 heteroatoms

selected from the group consisting of N, O, and S substituted with 0-3

R³¹;

15

R¹³, at each occurrence, is independently selected from

H, C₁₋₄ alkyl, C₂₋₄ alkenyl, and C₂₋₄ alkynyl;

alternatively, R¹² and R¹³ join to form a 5- or 6-membered ring optionally

20 substituted with -O- or -N(R¹⁴)-;

R¹⁴, at each occurrence, is independently selected from H and C₁₋₄ alkyl;

R³¹, at each occurrence, is independently selected from

25 H, OH, halo, CF₃, methyl, and ethyl;

R³³, at each occurrence, is independently selected from

H, OH, halo, CN, NO₂, CF₃, methyl, and ethyl;

- R⁴¹, at each occurrence, is independently selected from
H, CF₃, halo, OH, CO₂H, SO₂R⁴⁵, NR⁴⁶R⁴⁷, NO₂, CN, =O,
C₂₋₈ alkenyl, C₂₋₈ alkynyl, C₁₋₄ alkoxy, C₁₋₄ haloalkyl,
C₁₋₄ alkyl substituted with 0-1 R⁴³,
5 aryl substituted with 0-3 R⁴², and
5-10 membered heterocyclic ring system containing from 1-4 heteroatoms
selected from the group consisting of N, O, and S substituted with 0-3
R⁴⁴;
- 10 R⁴², at each occurrence, is independently selected from
H, CF₃, halo, OH, CO₂H, SO₂R⁴⁵, SR⁴⁵, NR⁴⁶R⁴⁷, OR⁴⁸, NO₂, CN,
CH(=NH)NH₂, NHC(=NH)NH₂,
C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₁₋₄ alkoxy, C₁₋₄ haloalkyl, C₃₋₆ cycloalkyl,
C₁₋₄ alkyl substituted with 0-1 R⁴³,
15 aryl substituted with 0-3 R⁴⁴, and
5-10 membered heterocyclic ring system containing from 1-4 heteroatoms
selected from the group consisting of N, O, and S substituted with 0-3
R⁴⁴;
- 20 R⁴³ is C₃₋₆-cycloalkyl or aryl substituted with 0-3 R⁴⁴;

R⁴⁴, at each occurrence, is independently selected from H, halo, -OH, NR⁴⁶R⁴⁷,
CO₂H, SO₂R⁴⁵, -CF₃, -OCF₃, -CN, -NO₂, C₁₋₄ alkyl, and C₁₋₄ alkoxy;

- 25 R⁴⁵ is C₁₋₄ alkyl;

R⁴⁶, at each occurrence, is independently selected from H and C₁₋₃ alkyl;

R⁴⁷, at each occurrence, is independently selected from H, C₁₋₄ alkyl,
-C(=O)NH(C₁₋₄ alkyl), -SO₂(C₁₋₄ alkyl),
-SO₂(phenyl), -C(=O)O(C₁₋₄ alkyl), -C(=O)(C₁₋₄ alkyl), and -C(=O)H;

5 R⁴⁸, at each occurrence, is independently selected from H, C₁₋₄ alkyl,
-C(=O)NH(C₁₋₄ alkyl), -C(=O)O(C₁₋₄ alkyl),
-C(=O)(C₁₋₄ alkyl), and -C(=O)H;

k is 1 or 2;

10 m is 0, 1, 2; and
n is 0, 1 or 2.

In a more preferred embodiment, the present invention provides the method as
15 defined in Claim 9 where in the compound administered:

X is -CH₂-;

R¹ is selected from

20 C₂₋₄ alkyl substituted with Z,
C₂₋₄ alkenyl substituted with Z,
C₂₋₄ alkynyl substituted with Z,
C₃₋₆ cycloalkyl substituted with Z,
aryl substituted with Z,
25 5-6 membered heterocyclic ring system containing at least one heteroatom
selected from the group consisting of N, O, and S, said heterocyclic
ring system substituted with Z;
C₂₋₄ alkyl substituted with 0-2 R², and
C₂₋₄ alkenyl substituted with 0-2 R²;

30

Z is selected from H,

- CH(OH)R²,
- C(ethylenedioxy)R²,
- OR²,
- 5 -SR²,
- NR²R³,
- C(O)R²,
- C(O)NR²R³,
- NR³C(O)R²,
- 10 -C(O)OR²,
- S(O)R²,
- S(O)₂R²,
- S(O)₂NR²R³, and -NR³S(O)₂R²;

- 15 R², at each occurrence, is independently selected from
- phenyl substituted with 0-5 R⁴²;
 - C₃-10 carbocyclic group substituted with 0-3 R⁴¹, and
 - 5-10 membered heterocyclic ring system containing from 1-4 heteroatoms
 - selected from the group consisting of N, O, and S substituted with 0-3
 - 20 R⁴¹;

- R³, at each occurrence, is independently selected from
- H, C₁-4 alkyl, C₂-4 alkenyl, C₂-4 alkynyl, and
 - C₁-4 alkoxy;

25

alternatively, R² and R³ join to form a 5- or 6-membered ring optionally substituted with -O- or -N(R⁴)-;

R⁴, at each occurrence, is independently selected from H, methyl, ethyl, propyl, and butyl;

R⁵ is H;

5

R^{6a} is selected from H, -OH, -CF₃, methyl, ethyl, propyl, butyl, methoxy, and, ethoxy;

R^{6b} is H;

10

R⁷, R⁸, and R⁹, at each occurrence, are independently selected from H, halo, -CF₃, -OCF₃, -OH, -OCH₃, -CN, -NO₂, C₁₋₄ alkyl, C₁₋₄ haloalkyl, C₁₋₄ alkoxy, (C₁₋₃ haloalkyl)oxy, and C₁₋₄ alkyl substituted with 0-2 R¹¹;

15

R¹¹ is selected from H, halo, -CF₃, -OCF₃, -OH, -OCH₃, -CN, -NO₂, C₁₋₄ alkyl, C₁₋₄ haloalkyl, C₁₋₄ alkoxy, and (C₁₋₃ haloalkyl)oxy;

20 R³³, at each occurrence, is independently selected from H, OH, halo, CF₃, and methyl;

R⁴¹, at each occurrence, is independently selected from

25 H, CF₃, halo, OH, CO₂H, SO₂R⁴⁵, NR⁴⁶R⁴⁷, NO₂, CN, =O, C₂₋₈ alkenyl, C₂₋₈ alkynyl, C₁₋₄ alkoxy, C₁₋₄ haloalkyl, C₁₋₄ alkyl substituted with 0-1 R⁴³, aryl substituted with 0-3 R⁴², and

5-10 membered heterocyclic ring system containing from 1-4 heteroatoms selected from the group consisting of N, O, and S substituted with 0-3 R⁴⁴;

- 5 R⁴², at each occurrence, is independently selected from
H, CF₃, halo, OH, CO₂H, SO₂R⁴⁵, SR⁴⁵, NR⁴⁶R⁴⁷, OR⁴⁸, NO₂, CN,
CH(=NH)NH₂, NHC(=NH)NH₂,
C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₁₋₄ alkoxy, C₁₋₄ haloalkyl, C₃₋₆ cycloalkyl,
C₁₋₄ alkyl substituted with 0-1 R⁴³,
10 aryl substituted with 0-3 R⁴⁴, and
5-10 membered heterocyclic ring system containing from 1-4 heteroatoms
selected from the group consisting of N, O, and S substituted with 0-3
R⁴⁴;
- 15 R⁴³ is cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, phenyl, or pyridyl, each
substituted with 0-3 R⁴⁴;

- R⁴⁴, at each occurrence, is independently selected from H, halo, -OH, NR⁴⁶R⁴⁷,
CO₂H, SO₂R⁴⁵, -CF₃, -OCF₃, -CN, -NO₂, methyl, ethyl, propyl, butyl,
20 methoxy, ethoxy, propoxy, and butoxy;

R⁴⁵ is methyl, ethyl, propyl, or butyl;

- R⁴⁶, at each occurrence, is independently selected from H, methyl, ethyl, propyl, and
25 butyl;

R⁴⁷, at each occurrence, is independently selected from
H, methyl, ethyl, n-propyl, i-propyl, n-butyl,
i-butyl, -C(=O)NH(methyl), -C(=O)NH(ethyl),

-SO₂(methyl), -SO₂(ethyl), -SO₂(phenyl),
-C(=O)O(methyl), -C(=O)O(ethyl), -C(=O)(methyl),
-C(=O)(ethyl), and -C(=O)H;

5 R⁴⁸, at each occurrence, is independently selected from
 H, methyl, ethyl, n-propyl, i-propyl, -C(=O)NH(methyl), -C(=O)NH(ethyl),
 -C(=O)O(methyl), -C(=O)O(ethyl), -C(=O)(methyl), -C(=O)(ethyl), and
 -C(=O)H;

10 k is 1;
 m is 0, 1, or 2; and
 n is 0, 1 or 2.

15 In a more preferred embodiment, the present invention provides the method as
defined in Claim 9 where in the compound administered:

X is -CH₂-;

20 R¹ is selected from
 ethyl substituted with Z,
 propyl substituted with Z,
 butyl substituted with Z,
 propenyl substituted with Z,
25 butenyl substituted with Z,
 ethyl substituted with R²,
 propyl substituted with R²,
 butyl substituted with R²,
 propenyl substituted with R², and
30 butenyl substituted with R²;

Z is selected from H,

- CH(OH)R²,
- OR²,
- 5 -SR²,
- NR²R³,
- C(O)R²,
- C(O)NR²R³,
- NR³C(O)R²,
- 10 -C(O)OR²,
- S(O)R²,
- S(O)₂R²,
- S(O)₂NR²R³, and -NR³S(O)₂R²;

15 R², at each occurrence, is independently selected from

- phenyl substituted with 0-3 R⁴²;
- naphthyl substituted with 0-3 R⁴²;
- cyclopropyl substituted with 0-3 R⁴¹;
- cyclobutyl substituted with 0-3 R⁴¹;
- 20 cyclopentyl substituted with 0-3 R⁴¹;
- cyclohexyl substituted with 0-3 R⁴¹;
- pyridyl substituted with 0-3 R⁴¹;
- indolyl substituted with 0-3 R⁴¹;
- indolinyll substituted with 0-3 R⁴¹;
- 25 benzimidazolyl substituted with 0-3 R⁴¹;
- benzotriazolyl substituted with 0-3 R⁴¹;
- benzothienyl substituted with 0-3 R⁴¹;
- benzofuranyl substituted with 0-3 R⁴¹;

phthalimid-1-yl substituted with 0-3 R⁴¹;
inden-2-yl substituted with 0-3 R⁴¹;
2,3-dihydro-1H-inden-2-yl substituted with 0-3 R⁴¹;
indazolyl substituted with 0-3 R⁴¹;
5 tetrahydroquinolinyl substituted with 0-3 R⁴¹; and
tetrahydro-isoquinolinyl substituted with 0-3 R⁴¹;

R³, at each occurrence, is independently selected from
H, methyl, and ethyl;

10

R⁵ is H;

R^{6a} is selected from H, -OH, methyl, and methoxy;

15 R^{6b} is H;

R⁷, R⁸, and R⁹, at each occurrence, are independently selected from H, F, Cl, methyl,
ethyl, methoxy, -CF₃,
and -OCF₃;

20

R⁴¹, at each occurrence, is independently selected from
H, F, Cl, Br, OH, CF₃, NO₂, CN, =O, methyl, ethyl, propyl, butyl, methoxy,
and ethoxy;

25 R⁴², at each occurrence, is independently selected from
H, F, Cl, Br, OH, CF₃, SO₂R⁴⁵, SR⁴⁵, NR⁴⁶R⁴⁷, OR⁴⁸, NO₂, CN, =O,
methyl, ethyl, propyl, butyl, methoxy, and ethoxy;

R⁴⁵ is methyl, ethyl, propyl, or butyl;

R⁴⁶, at each occurrence, is independently selected from H, methyl, ethyl, propyl, and butyl;

5 R⁴⁷, at each occurrence, is independently selected from
H, methyl, ethyl, n-propyl, i-propyl, n-butyl,
i-butyl, -C(=O)NH(methyl), -C(=O)NH(ethyl),
-SO₂(methyl), -SO₂(ethyl), -SO₂(phenyl),
-C(=O)O(methyl), -C(=O)O(ethyl), -C(=O)(methyl),
10 -C(=O)(ethyl), and -C(=O)H;

R⁴⁸, at each occurrence, is independently selected from
H, methyl, ethyl, n-propyl, i-propyl, -C(=O)NH(methyl), -C(=O)NH(ethyl),
-C(=O)O(methyl), -C(=O)O(ethyl), -C(=O)(methyl), -C(=O)(ethyl), and
15 -C(=O)H;

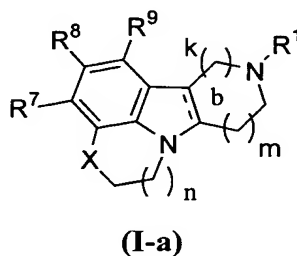
k is 1;

m is 0, 1, or 2; and

n is 0, 1 or 2.

20

In a more preferred embodiment, the present invention provides the method as defined in Claim 9 where the compound administered is a compound of Formula (I-a):



25

wherein:

b is a single bond;

X is -CH₂-, CH(OH)-, or -C(=O)-

5

R¹ is selected from

- (CH₂)₃C(=O)(4-fluoro-phenyl),
- (CH₂)₃C(=O)(4-bromo-phenyl),
- (CH₂)₃C(=O)(4-methyl-phenyl),
- 10 -(CH₂)₃C(=O)(4-methoxy-phenyl),
- (CH₂)₃C(=O)(4-(3,4-dichloro-phenyl)phenyl),
- (CH₂)₃C(=O)(3-methyl-4-fluoro-phenyl),
- (CH₂)₃C(=O)(2,3-dimethoxy-phenyl),
- (CH₂)₃C(=O)(phenyl),
- 15 -(CH₂)₃C(=O)(4-chloro-phenyl),
- (CH₂)₃C(=O)(3-methyl-phenyl),
- (CH₂)₃C(=O)(4-t-butyl-phenyl),
- (CH₂)₃C(=O)(3,4-difluoro-phenyl),
- (CH₂)₃C(=O)(2-methoxy-5-fluoro-phenyl),
- 20 -(CH₂)₃C(=O)(4-fluoro-1-naphthyl),
- (CH₂)₃C(=O)(benzyl),
- (CH₂)₃C(=O)(4-pyridyl),
- (CH₂)₃C(=O)(3-pyridyl),
- (CH₂)₃CH(OH)(4-fluoro-phenyl),
- 25 -(CH₂)₃CH(OH)(4-pyridyl),
- (CH₂)₃CH(OH)(2,3-dimethoxy-phenyl),
- (CH₂)₃S(3-fluoro-phenyl),
- (CH₂)₃S(4-fluoro-phenyl),
- (CH₂)₃S(=O)(4-fluoro-phenyl),

- (CH₂)₃SO₂(3-fluoro-phenyl),
- (CH₂)₃SO₂(4-fluoro-phenyl),
- (CH₂)₃O(4-fluoro-phenyl),
- (CH₂)₃O(phenyl),
- 5 -(CH₂)₃O(3-pyridyl),
- (CH₂)₃O(4-pyridyl),
- (CH₂)₃O(2-NH₂-phenyl),
- (CH₂)₃O(2-NH₂-5-F-phenyl),
- (CH₂)₃O(2-NH₂-4-F-phenyl),
- 10 -(CH₂)₃O(2-NH₂-3-F-phenyl),
- (CH₂)₃O(2-NH₂-4-Cl-phenyl),
- (CH₂)₃O(2-NH₂-4-OH-phenyl),
- (CH₂)₃O(2-NH₂-4-Br-phenyl),
- (CH₂)₃O(2-NHC(=O)Me-4-F-phenyl),
- 15 -(CH₂)₃O(2-NHC(=O)Me-phenyl),
- (CH₂)₃NH(4-fluoro-phenyl),
- (CH₂)₃N(methyl)(4-fluoro-phenyl),
- (CH₂)₃CO₂(ethyl),
- (CH₂)₃C(=O)N(methyl)(methoxy),
- 20 -(CH₂)₃C(=O)NH(4-fluoro-phenyl),
- (CH₂)₂NHC(=O)(phenyl),
- (CH₂)₂NMeC(=O)(phenyl),
- (CH₂)₂NHC(=O)(2-fluoro-phenyl),
- (CH₂)₂NMeC(=O)(2-fluoro-phenyl),
- 25 -(CH₂)₂NHC(=O)(4-fluoro-phenyl),
- (CH₂)₂NMeC(=O)(4-fluoro-phenyl),
- (CH₂)₂NHC(=O)(2,4-difluoro-phenyl),
- (CH₂)₂NMeC(=O)(2,4-difluoro-phenyl),
- (CH₂)₃(3-indolyl),

- (CH₂)₃(1-methyl-3-indolyl),
- (CH₂)₃(1-indolyl),
- (CH₂)₃(1-indoliny),
- (CH₂)₃(1-benzimidazolyl),
- 5 - (CH₂)₃(1H-1,2,3-benzotriazol-1-yl),
- (CH₂)₃(1H-1,2,3-benzotriazol-2-yl),
- (CH₂)₂(1H-1,2,3-benzotriazol-1-yl),
- (CH₂)₂(1H-1,2,3-benzotriazol-2-yl),
- (CH₂)₃(3,4 dihydro-1(2H)-quinoliny),
- 10 - (CH₂)₂C(=O)(4-fluoro-phenyl),
- (CH₂)₂C(=O)NH(4-fluoro-phenyl),
- CH₂CH₂(3-indolyl),
- CH₂CH₂(1-phthalimidyl),
- (CH₂)₄C(=O)N(methyl)(methoxy),
- 15 - (CH₂)₄CO₂(ethyl),
- (CH₂)₄C(=O)(phenyl),
- (CH₂)₄(cyclohexyl),
- (CH₂)₃CH(phenyl)₂,
- CH₂CH₂CH=C(phenyl)₂,
- 20 - CH₂CH₂CH=CMe(4-F-phenyl),
- (CH₂)₃CH(4-fluoro-phenyl)₂,
- CH₂CH₂CH=C(4-fluoro-phenyl)₂,
- (CH₂)₂(2,3-dihydro-1H-inden-2-yl),
- (CH₂)₃C(=O)(2-NH₂-phenyl),
- 25 - (CH₂)₃C(=O)(2-NH₂-5-F-phenyl),
- (CH₂)₃C(=O)(2-NH₂-4-F-phenyl),
- (CH₂)₃C(=O)(2-NH₂-3-F-phenyl),
- (CH₂)₃C(=O)(2-NH₂-4-Cl-phenyl),
- (CH₂)₃C(=O)(2-NH₂-4-OH-phenyl),

- (CH₂)₃C(=O)(2-NH₂-4-Br-phenyl),
- (CH₂)₃(1H-indazol-3-yl),
- (CH₂)₃(5-F-1H-indazol-3-yl),
- (CH₂)₃(7-F-1H-indazol-3-yl),
- 5 - (CH₂)₃(6-Cl-1H-indazol-3-yl),
- (CH₂)₃(6-Br-1H-indazol-3-yl),
- (CH₂)₃C(=O)(2-NHMe-phenyl),
- (CH₂)₃(1-benzothien-3-yl),
- (CH₂)₃(6-F-1H-indol-1-yl),
- 10 - (CH₂)₃(5-F-1H-indol-1-yl),
- (CH₂)₃(6-F-2,3-dihydro-1H-indol-1-yl),
- (CH₂)₃(5-F-2,3-dihydro-1H-indol-1-yl),
- (CH₂)₃(6-F-1H-indol-3-yl),
- (CH₂)₃(5-F-1H-indol-3-yl),
- 15 - (CH₂)₃(5-F-1H-indol-3-yl),
- (CH₂)₃(9H-purin-9-yl),
- (CH₂)₃(7H-purin-7-yl),
- (CH₂)₃(6-F-1H-indazol-3-yl),
- (CH₂)₃C(=O)(2-NHSO₂Me-4-F-phenyl),
- 20 - (CH₂)₃C(=O)(2-NHC(=O)Me-4-F-phenyl),
- (CH₂)₃C(=O)(2-NHC(=O)Me-phenyl),
- (CH₂)₃C(=O)(2-NHCO₂Et-4-F-phenyl),
- (CH₂)₃C(=O)(2-NHC(=O)NEt-4-F-phenyl),
- (CH₂)₃C(=O)(2-NHCHO-4-F-phenyl),
- 25 - (CH₂)₃C(=O)(2-OH-4-F-phenyl),
- (CH₂)₃C(=O)(2-MeS-4-F-phenyl),
- (CH₂)₃C(=O)(2-NHSO₂Me-4-F-phenyl),
- (CH₂)₂C(Me)CO₂Me,
- (CH₂)₂C(Me)CH(OH)(4-F-phenyl)₂,

-(CH₂)₂C(Me)CH(OH)(4-Cl-phenyl)₂,

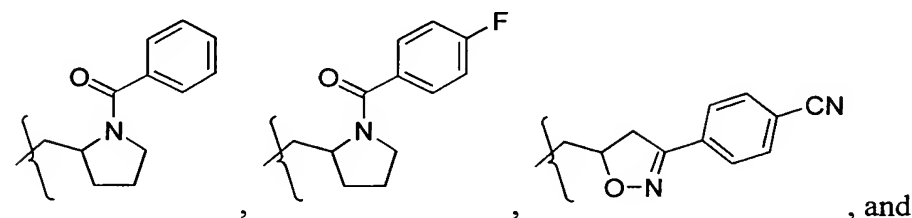
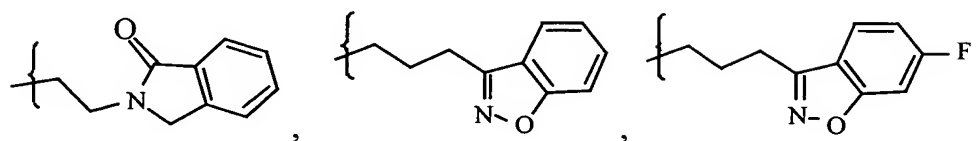
-(CH₂)₂C(Me)C(=O)(4-F-phenyl),

-(CH₂)₂C(Me)C(=O)(2-MeO-4-F-phenyl),

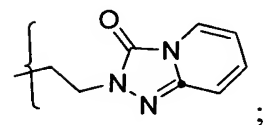
-(CH₂)₂C(Me)C(=O)(3-Me-4-F-phenyl),

5 -(CH₂)₂C(Me)C(=O)(2-Me-phenyl),

-(CH₂)₂C(Me)C(=O)phenyl,



10



R⁷, R⁸, and R⁹, at each occurrence, are independently selected from

15 hydrogen, fluoro, chloro, bromo, cyano, methyl, ethyl, propyl, isopropyl, butyl,

t-butyl, nitro, trifluoromethyl, methoxy, ethoxy, isopropoxy,

trifluoromethoxy, phenyl, benzyl,

HC(=O)-, methylC(=O)-, ethylC(=O)-, propylC(=O)-, isopropylC(=O)-, n-

butylC(=O)-, isobutylC(=O)-, secbutylC(=O)-, tertbutylC(=O)-,

20

phenylC(=O)-,

methylC(=O)NH-, ethylC(=O)NH-, propylC(=O)NH-, isopropylC(=O)NH-,

n-butylC(=O)NH-, isobutylC(=O)NH-, secbutylC(=O)NH-,

tertbutylC(=O)NH-, phenylC(=O)NH-,

methylamino-, ethylamino-, propylamino-, isopropylamino-, n-butylamino-,
isobutylamino-, secbutylamino-, tertbutylamino-, phenylamino-,

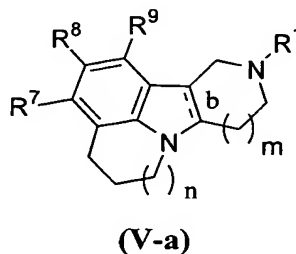
provided that two of substituents R^7 , R^8 , and R^9 , are independently selected
5 from hydrogen, fluoro, chloro, bromo, cyano, methyl, ethyl, propyl,
isopropyl, butyl, t-butyl, nitro, trifluoromethyl, methoxy, ethoxy,
isopropoxy, and trifluoromethoxy;

k is 1 or 2;

10 m is 1 or 2; and

n is 0, 1 or 2.

In a more preferred embodiment, the present invention provides the method as
15 defined in Claim 13 where the compound administered is a compound of Formula (V-a):



20

wherein:

b is a single bond, wherein the bridge hydrogens are in a cis position;

25 R^1 is selected from

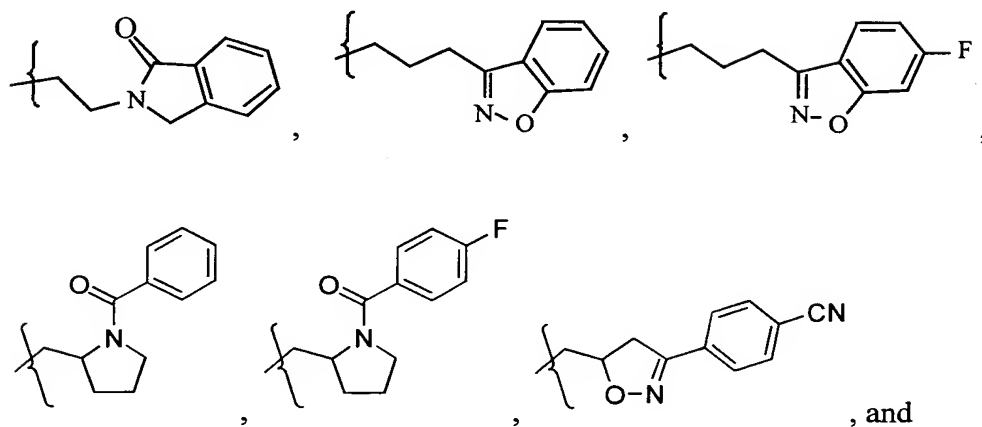
- (CH₂)₃C(=O)(4-fluoro-phenyl),
- (CH₂)₃C(=O)(4-bromo-phenyl),
- (CH₂)₃C(=O)(4-methyl-phenyl),

- $(\text{CH}_2)_3\text{C}(=\text{O})(4\text{-methoxy-phenyl})$,
- $(\text{CH}_2)_3\text{C}(=\text{O})(4\text{-(3,4-dichloro-phenyl)phenyl})$,
- $(\text{CH}_2)_3\text{C}(=\text{O})(3\text{-methyl-4-fluoro-phenyl})$,
- $(\text{CH}_2)_3\text{C}(=\text{O})(2,3\text{-dimethoxy-phenyl})$,
- 5 - $(\text{CH}_2)_3\text{C}(=\text{O})(\text{phenyl})$,
- $(\text{CH}_2)_3\text{C}(=\text{O})(4\text{-chloro-phenyl})$,
- $(\text{CH}_2)_3\text{C}(=\text{O})(3\text{-methyl-phenyl})$,
- $(\text{CH}_2)_3\text{C}(=\text{O})(4\text{-t-butyl-phenyl})$,
- $(\text{CH}_2)_3\text{C}(=\text{O})(3,4\text{-difluoro-phenyl})$,
- 10 - $(\text{CH}_2)_3\text{C}(=\text{O})(2\text{-methoxy-5-fluoro-phenyl})$,
- $(\text{CH}_2)_3\text{C}(=\text{O})(4\text{-fluoro-1-naphthyl})$,
- $(\text{CH}_2)_3\text{C}(=\text{O})(\text{benzyl})$,
- $(\text{CH}_2)_3\text{C}(=\text{O})(4\text{-pyridyl})$,
- $(\text{CH}_2)_3\text{C}(=\text{O})(3\text{-pyridyl})$,
- 15 - $(\text{CH}_2)_3\text{CH}(\text{OH})(4\text{-fluoro-phenyl})$,
- $(\text{CH}_2)_3\text{CH}(\text{OH})(4\text{-pyridyl})$,
- $(\text{CH}_2)_3\text{CH}(\text{OH})(2,3\text{-dimethoxy-phenyl})$,
- $(\text{CH}_2)_3\text{S}(3\text{-fluoro-phenyl})$,
- $(\text{CH}_2)_3\text{S}(4\text{-fluoro-phenyl})$,
- 20 - $(\text{CH}_2)_3\text{S}(=\text{O})(4\text{-fluoro-phenyl})$,
- $(\text{CH}_2)_3\text{SO}_2(3\text{-fluoro-phenyl})$,
- $(\text{CH}_2)_3\text{SO}_2(4\text{-fluoro-phenyl})$,
- $(\text{CH}_2)_3\text{O}(4\text{-fluoro-phenyl})$,
- $(\text{CH}_2)_3\text{O}(\text{phenyl})$,
- 25 - $(\text{CH}_2)_3\text{NH}(4\text{-fluoro-phenyl})$,
- $(\text{CH}_2)_3\text{N}(\text{methyl})(4\text{-fluoro-phenyl})$,
- $(\text{CH}_2)_3\text{CO}_2(\text{ethyl})$,
- $(\text{CH}_2)_3\text{C}(=\text{O})\text{N}(\text{methyl})(\text{methoxy})$,
- $(\text{CH}_2)_3\text{C}(=\text{O})\text{NH}(4\text{-fluoro-phenyl})$,

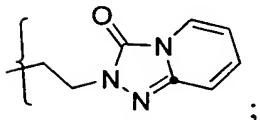
- (CH₂)₂NHC(=O)(phenyl),
- (CH₂)₂NMeC(=O)(phenyl),
- (CH₂)₂NHC(=O)(2-fluoro-phenyl),
- (CH₂)₂NMeC(=O)(2-fluoro-phenyl),
- 5 - (CH₂)₂NHC(=O)(4-fluoro-phenyl),
- (CH₂)₂NMeC(=O)(4-fluoro-phenyl),
- (CH₂)₂NHC(=O)(2,4-difluoro-phenyl),
- (CH₂)₂NMeC(=O)(2,4-difluoro-phenyl),
- (CH₂)₃(3-indolyl),
- 10 - (CH₂)₃(1-methyl-3-indolyl),
- (CH₂)₃(1-indolyl),
- (CH₂)₃(1-indolyl),
- (CH₂)₃(1-benzimidazolyl),
- (CH₂)₃(1H-1,2,3-benzotriazol-1-yl),
- 15 - (CH₂)₃(1H-1,2,3-benzotriazol-2-yl),
- (CH₂)₂(1H-1,2,3-benzotriazol-1-yl),
- (CH₂)₂(1H-1,2,3-benzotriazol-2-yl),
- (CH₂)₃(3,4 dihydro-1(2H)-quinolyl),
- (CH₂)₂C(=O)(4-fluoro-phenyl),
- 20 - (CH₂)₂C(=O)NH(4-fluoro-phenyl),
- CH₂CH₂(3-indolyl),
- CH₂CH₂(1-phthalimidyl),
- (CH₂)₄C(=O)N(methyl)(methoxy),
- (CH₂)₄CO₂(ethyl),
- 25 - (CH₂)₄C(=O)(phenyl),
- (CH₂)₄(cyclohexyl),
- (CH₂)₃CH(phenyl)₂,
- CH₂CH₂CH=C(phenyl)₂,
- CH₂CH₂CH=CMe(4-F-phenyl),

- (CH₂)₃CH(4-fluoro-phenyl)₂,
- CH₂CH₂CH=C(4-fluoro-phenyl)₂,
- (CH₂)₂(2,3-dihydro-1H-inden-2-yl),
- (CH₂)₃C(=O)(2-NH₂-phenyl),
- 5 - (CH₂)₃C(=O)(2-NH₂-5-F-phenyl),
- (CH₂)₃C(=O)(2-NH₂-4-F-phenyl),
- (CH₂)₃C(=O)(2-NH₂-3-F-phenyl),
- (CH₂)₃C(=O)(2-NH₂-4-Cl-phenyl),
- (CH₂)₃C(=O)(2-NH₂-4-OH-phenyl),
- 10 - (CH₂)₃C(=O)(2-NH₂-4-Br-phenyl),
- (CH₂)₃(1H-indazol-3-yl),
- (CH₂)₃(5-F-1H-indazol-3-yl),
- (CH₂)₃(7-F-1H-indazol-3-yl),
- (CH₂)₃(6-Cl-1H-indazol-3-yl),
- 15 - (CH₂)₃(6-Br-1H-indazol-3-yl),
- (CH₂)₃C(=O)(2-NHMe-phenyl),
- (CH₂)₃(1-benzothien-3-yl),
- (CH₂)₃(6-F-1H-indol-1-yl),
- (CH₂)₃(5-F-1H-indol-1-yl),
- 20 - (CH₂)₃(6-F-2,3-dihydro-1H-indol-1-yl),
- (CH₂)₃(5-F-2,3-dihydro-1H-indol-1-yl),
- (CH₂)₃(6-F-1H-indol-3-yl),
- (CH₂)₃(5-F-1H-indol-3-yl),
- (CH₂)₃(5-F-1H-indol-3-yl),
- 25 - (CH₂)₃(9H-purin-9-yl),
- (CH₂)₃(7H-purin-7-yl),
- (CH₂)₃(6-F-1H-indazol-3-yl),
- (CH₂)₃C(=O)(2-NHSO₂Me-4-F-phenyl),
- (CH₂)₃C(=O)(2-NHC(=O)Me-4-F-phenyl),

- (CH₂)₃C(=O)(2-NHC(=O)Me-4-F-phenyl),
 -(CH₂)₃C(=O)(2-NHCO₂Et-4-F-phenyl),
 -(CH₂)₃C(=O)(2-NHC(=O)NHEt-4-F-phenyl),
 -(CH₂)₃C(=O)(2-NHCHO-4-F-phenyl),
 5 -(CH₂)₃C(=O)(2-OH-4-F-phenyl),
 -(CH₂)₃C(=O)(2-MeS-4-F-phenyl),
 -(CH₂)₃C(=O)(2-NHSO₂Me-4-F-phenyl),
 -(CH₂)₂C(Me)CO₂Me,
 -(CH₂)₂C(Me)CH(OH)(4-F-phenyl)₂,
 10 -(CH₂)₂C(Me)CH(OH)(4-Cl-phenyl)₂,
 -(CH₂)₂C(Me)C(=O)(4-F-phenyl),
 -(CH₂)₂C(Me)C(=O)(2-MeO-4-F-phenyl),
 -(CH₂)₂C(Me)C(=O)(3-Me-4-F-phenyl),
 -(CH₂)₂C(Me)C(=O)(2-Me-phenyl),
 15 -(CH₂)₂C(Me)C(=O)phenyl,



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R⁷, R⁸, and R⁹, at each occurrence, are independently selected from hydrogen, fluoro, chloro, bromo, cyano, methyl, ethyl, propyl, isopropyl, butyl, t-butyl, nitro, trifluoromethyl, methoxy, ethoxy, isopropoxy, trifluoromethoxy, methylC(=O)-, ethylC(=O)-, propylC(=O)-, isopropylC(=O)-, methylC(=O)NH-, ethylC(=O)NH-, propylC(=O)NH-, isopropylC(=O)NH-, methylamino-, ethylamino-, propylamino-, and isopropylamino-,

provided that two of substituents R⁷, R⁸, and R⁹, are independently selected from hydrogen, fluoro, chloro, methyl, trifluoromethyl, methoxy, and trifluoromethoxy;

m is 1 or 2; and

n is 0, 1 or 2.

In a more preferred embodiment, the present invention provides the method as defined in Claim 1 where the compound administered is selected from the group:

(±)-*cis*-9-(cyclopropylcarbonyl)-4,5,6a,7,8,9,10,10a-octahydropyrido[4,3-*b*]pyrrolo[3,2,1-*hi*]indole;

(±)-*cis*-9-isobutyryl-4,5,6a,7,8,9,10,10a-octahydropyrido[4,3-*b*]pyrrolo[3,2,1-*hi*]indole;

tert-butyl (±)-*cis*-2-(2-chlorophenyl)-4,5,7,8,10,10a-hexahydropyrido[4,3-*b*]pyrrolo[3,2,1-*hi*]indole-9(6a*H*)-carboxylate;

tert-butyl (±)-*cis*-2-(2,4-dichlorophenyl)-4,5,7,8,10,10a-hexahydropyrido[4,3-*b*]pyrrolo[3,2,1-*hi*]indole-9(6a*H*)-carboxylate;

tert-butyl (±)-*cis*-2-(3,4-dichlorophenyl)-4,5,7,8,10,10a-hexahydropyrido[4,3-*b*]pyrrolo[3,2,1-*hi*]indole-9(6a*H*)-carboxylate;

5 *tert*-butyl (±)-*cis*-2-(2,3-dichlorophenyl)-4,5,7,8,10,10a-hexahydropyrido[4,3-*b*]pyrrolo[3,2,1-*hi*]indole-9(6a*H*)-carboxylate;

tert-butyl (±)-*cis*-2-[2-chloro-4-(trifluoromethyl)phenyl]-4,5,7,8,10,10a-hexahydropyrido[4,3-*b*]pyrrolo[3,2,1-*hi*]indole-9(6a*H*)-carboxylate;

10 *tert*-butyl (±)-*cis*-2-(2-chloro-4-methoxyphenyl)-4,5,7,8,10,10a-hexahydropyrido[4,3-*b*]pyrrolo[3,2,1-*hi*]indole-9(6a*H*)-carboxylate;

tert-butyl (±)-*cis*-2-(5-isopropyl-2-methoxyphenyl)-4,5,7,8,10,10a-hexahydropyrido[4,3-*b*]pyrrolo[3,2,1-*hi*]indole-9(6a*H*)-carboxylate;

15 *tert*-butyl (±)-*cis*-2-(3-fluorophenyl)-4,5,7,8,10,10a-hexahydropyrido[4,3-*b*]pyrrolo[3,2,1-*hi*]indole-9(6a*H*)-carboxylate;

20 *tert*-butyl (±)-*cis*-2-(2,4-dimethoxyphenyl)-4,5,7,8,10,10a-hexahydropyrido[4,3-*b*]pyrrolo[3,2,1-*hi*]indole-9(6a*H*)-carboxylate;

(±)-*cis*-2-(2-chlorophenyl)-4,5,6a,7,8,9,10,10a-octahydropyrido[4,3-*b*]pyrrolo[3,2,1-*hi*]indole;

25 (±)-*cis*-2-(2,4-dichlorophenyl)-4,5,6a,7,8,9,10,10a-octahydropyrido[4,3-*b*]pyrrolo[3,2,1-*hi*]indole;

(±)-*cis*-2-(3,4-dichlorophenyl)-4,5,6a,7,8,9,10,10a-octahydropyrido[4,3-*b*]pyrrolo[3,2,1-*hi*]indole;

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- (±)-*cis*-2-(2,3-dichlorophenyl)-4,5,6a,7,8,9,10,10a-octahydropyrido[4,3-*b*]pyrrolo[3,2,1-*hi*]indole;
- 5 (±)-*cis*-2-[2-chloro-4-(trifluoromethyl)phenyl]-4,5,6a,7,8,9,10,10a-octahydropyrido[4,3-*b*]pyrrolo[3,2,1-*hi*]indole;
- (±)-*cis*-2-(2-chloro-4-methoxyphenyl)-4,5,6a,7,8,9,10,10a-octahydropyrido[4,3-*b*]pyrrolo[3,2,1-*hi*]indole;
- 10 (±)-*cis*-2-(4-isopropyl-2-methoxyphenyl)-4,5,6a,7,8,9,10,10a-octahydropyrido[4,3-*b*]pyrrolo[3,2,1-*hi*]indole;
- (±)-*cis*-2-(3-fluorophenyl)-4,5,6a,7,8,9,10,10a-octahydropyrido[4,3-*b*]pyrrolo[3,2,1-*hi*]indole;
- 15 (±)-*cis*-2-(2,4-dimethoxyphenyl)-4,5,6a,7,8,9,10,10a-octahydropyrido[4,3-*b*]pyrrolo[3,2,1-*hi*]indole;
- tert*-butyl (±)-*cis*-5,6,8,9,11,11a-hexahydro-4*H*-pyrido[3',4':4,5]pyrrolo[3,2,1-*ij*]quinoline-10(7*aH*)-carboxylate;
- 20 *tert*-butyl (±)-*cis*-2-bromo-5,6,8,9,11,11a-hexahydro-4*H*-pyrido[3',4':4,5]pyrrolo[3,2,1-*ij*]quinoline-10(7*aH*)-carboxylate;
- 25 *tert*-butyl (±)-*cis*-2-(2,3-dichlorophenyl)-5,6,8,9,11,11a-hexahydro-4*H*-pyrido[3',4':4,5]pyrrolo[3,2,1-*ij*]quinoline-10(7*aH*)-carboxylate;
- tert*-butyl (±)-*cis*-2-(3,4-dichlorophenyl)-5,6,8,9,11,11a-hexahydro-4*H*-pyrido[3',4':4,5]pyrrolo[3,2,1-*ij*]quinoline-10(7*aH*)-carboxylate;
- 30

- tert*-butyl (±)-*cis*-2-[2-chloro-4-(trifluoromethyl)phenyl]-5,6,8,9,11,11a-hexahydro-4*H*-pyrido[3',4':4,5]pyrrolo[3,2,1-*ij*]quinoline-10(7*aH*)-carboxylate;
- 5 (±)-*cis*-2-(2,3-dichlorophenyl)-5,6,7a,8,9,10,11,11a-octahydro-4*H*-pyrido[3',4':4,5]pyrrolo[3,2,1-*ij*]quinoline;
- (±)-*cis*-2-(3,4-dichlorophenyl)-5,6,7a,8,9,10,11,11a-octahydro-4*H*-pyrido[3',4':4,5]pyrrolo[3,2,1-*ij*]quinoline;
- 10 (±)-*cis*-2-[2-chloro-4-(trifluoromethyl)phenyl]-5,6,7a,8,9,10,11,11a-octahydro-4*H*-pyrido[3',4':4,5]pyrrolo[3,2,1-*ij*]quinoline;
- 4-((±)-*cis*-2-(2-chlorophenyl)-4,5,7,8,10,10a-hexahydropyrido[4,3-*b*]pyrrolo[3,2,1-*hi*]indol-9(6*aH*)-yl)-1-(4-fluorophenyl)-1-butanone;
- 15 4-((±)-*cis*-2-(2,4-dichlorophenyl)-4,5,7,8,10,10a-hexahydropyrido[4,3-*b*]pyrrolo[3,2,1-*hi*]indol-9(6*aH*)-yl)-1-(4-fluorophenyl)-1-butanone;
- 20 4-((±)-*cis*-5,6,8,9,11,11a-hexahydro-4*H*-pyrido[3',4':4,5]pyrrolo[3,2,1-*ij*]qionolin-10(7*aH*)-yl)-1-(4-fluorophenyl)-1-butanone;
- 4-((±)-*cis*-4,5,7,8,10,10a-hexahydropyrido[4.3-*b*]pyrrolo[3,2,1-*hi*]indol-9(6*aH*)-yl)-1-(4-fluorophenyl)-1-butanone;
- 25 (6*aS*,10*aR*)-2-(2-fluoro-4-methoxyphenyl)-4,5,6a,7,8,9,10,10a-octahydropyrido[4,3-*b*]pyrrolo[3,2,1-*hi*]indole;
- tert*-butyl (6*aS*,10*aR*)-2-[4-ethoxy-2-(trifluoromethyl)phenyl]-4,5,7,8,10,10a-hexahydropyrido [4,3-*b*]pyrrolo[3,2,1-*hi*]indole-9(6*aH*)-carboxylate;
- 30

- (6a*S*,10a*R*)-2-[4-ethoxy-2-(trifluoromethyl)phenyl]-4,5,6a,7,8,9,10,10a-octahydropyrido [4,3-*b*]pyrrolo[3,2,1-*hi*]indole;
- 5 *tert*-butyl (6a*S*,10a*R*)-2-(4-chloro-2-fluorophenyl)-4,5,7,8,10,10a-hexahydropyrido[4,3-*b*]pyrrolo[3,2,1-*hi*]indole-9(6a*H*)-carboxylate;
- (6a*S*,10a*R*)- 2-(4-chloro-2-fluorophenyl)-4,5,6a,7,8,9,10,10a-octahydropyrido [4,3-*b*]pyrrolo[3,2,1-*hi*]indole;
- 10 *tert*-butyl (6a*S*,10a*R*)-2-[4-isopropoxy-2-(trifluoromethyl)phenyl]-4,5,7,8,10,10a-hexahydropyrido[4,3-*b*]pyrrolo[3,2,1-*hi*]indole-9(6a*H*)-carboxylate;
- (6a*S*,10a*R*)-2-[4-isopropoxy-2-(trifluoromethyl)phenyl]-4,5,6a,7,8,9,10,10a-octahydropyrido [4,3-*b*]pyrrolo[3,2,1-*hi*]indole;
- 15 *tert*-butyl (6a*S*,10a*R*)-2-[4-methoxy-2-(trifluoromethyl)phenyl]-4,5,7,8,10,10a-hexahydropyrido[4,3-*b*]pyrrolo[3,2,1-*hi*]indole-9(6a*H*)-carboxylate;
- (6a*S*,10a*R*)-2-[4-methoxy-2-(trifluoromethyl)phenyl]-4,5,6a,7,8,9,10,10a-octahydropyrido [4,3-*b*]pyrrolo[3,2,1-*hi*]indole;
- 20 *tert*-butyl (6a*S*,10a*R*)-2-phenyl-4,5,7,8,10,10a-hexahydropyrido[4,3-*b*]pyrrolo[3,2,1-*hi*]indole-9(6a*H*)-carboxylate;
- 25 (6a*S*,10a*R*)-2-phenyl-4,5,6a,7,8,9,10,10a-octahydropyrido [4,3-*b*]pyrrolo[3,2,1-*hi*]indole;
- tert*-butyl (6a*S*,10a*R*)-2-(2-methylphenyl)-4,5,7,8,10,10a-hexahydropyrido[4,3-*b*]pyrrolo[3,2,1-*hi*]indole-9(6a*H*)-carboxylate;
- 30

(6a*S*,10a*R*)-2-(2-methylphenyl)-4,5,6a,7,8,9,10,10a-octahydropyrido [4,3-*b*]pyrrolo[3,2,1-*hi*]indole;

5 *tert*-butyl (6a*S*,10a*R*)-2-[2-(trifluoromethyl)phenyl]-4,5,7,8,10,10a-hexahydropyrido[4,3-*b*]pyrrolo[3,2,1-*hi*]indole-9(6a*H*)-carboxylate;

(6a*S*,10a*R*)-2-[2-(trifluoromethyl)phenyl]-4,5,6a,7,8,9,10,10a-octahydropyrido [4,3-*b*]pyrrolo[3,2,1-*hi*]indole;

10 *tert*-butyl (6a*S*,10a*R*)-2-(3,4-dimethoxyphenyl)-4,5,7,8,10,10a-hexahydropyrido[4,3-*b*]pyrrolo[3,2,1-*hi*]indole-9(6a*H*)-carboxylate;

(6a*S*,10a*R*)-2-(3,4-dimethoxyphenyl)-4,5,6a,7,8,9,10,10a-octahydropyrido [4,3-*b*]pyrrolo[3,2,1-*hi*]indole;

15 *tert*-butyl (6a*S*,10a*R*)-2-(2,5-dichlorophenyl)-4,5,7,8,10,10a-hexahydropyrido[4,3-*b*]pyrrolo[3,2,1-*hi*]indole-9(6a*H*)-carboxylate;

20 (6a*S*,10a*R*)-2-(2,5-dichlorophenyl)-4,5,6a,7,8,9,10,10a-octahydropyrido [4,3-*b*]pyrrolo[3,2,1-*hi*]indole;

tert-butyl (6a*S*,10a*R*)-2-(3,5-dichlorophenyl)-4,5,7,8,10,10a-hexahydropyrido[4,3-*b*]pyrrolo[3,2,1-*hi*]indole-9(6a*H*)-carboxylate;

25 (6a*S*,10a*R*)-2-(3,5-dichlorophenyl)-4,5,6a,7,8,9,10,10a-octahydropyrido [4,3-*b*]pyrrolo[3,2,1-*hi*]indole;

tert-butyl (6a*S*,10a*R*)-2-(2-isopropyl-4-methoxyphenyl)-4,5,7,8,10,10a-hexahydropyrido[4,3-*b*]pyrrolo[3,2,1-*hi*]indole-9(6a*H*)-carboxylate;

30 (6a*S*,10a*R*)-2-(2-isopropyl-4-methoxyphenyl)-4,5,6a,7,8,9,10,10a-octahydropyrido [4,3-*b*]pyrrolo[3,2,1-*hi*]indole;

- tert*-butyl (6a*S*,10a*R*)-2-(5-fluoro-4-methoxy-2-methylphenyl)-4,5,7,8,10,10a-hexahydropyrido[4,3-*b*]pyrrolo[3,2,1-*hi*]indole-9(6a*H*)-carboxylate;
- 5 (6a*S*,10a*R*)-2-(5-fluoro-4-methoxy-2-methylphenyl)-4,5,6a,7,8,9,10,10a-octahydropyrido [4,3-*b*]pyrrolo[3,2,1-*hi*]indole;
- tert*-butyl (6a*S*,10a*R*)-2-(4-methoxy-2-methylphenyl)-4,5,7,8,10,10a-hexahydropyrido[4,3-*b*]pyrrolo[3,2,1-*hi*]indole-9(6a*H*)-carboxylate;
- 10 (6a*S*,10a*R*)-2-(4-methoxy-2-methylphenyl)-4,5,6a,7,8,9,10,10a-octahydropyrido [4,3-*b*]pyrrolo[3,2,1-*hi*]indole;
- tert*-butyl (6a*S*,10a*R*)-2-(2-chloro-4-methoxyphenyl)-4,5,7,8,10,10a-hexahydropyrido[4,3-*b*]pyrrolo[3,2,1-*hi*]indole-9(6a*H*)-carboxylate;
- 15 (6a*S*,10a*R*)-2-(2-chloro-4-methoxyphenyl)-4,5,6a,7,8,9,10,10a-octahydropyrido [4,3-*b*]pyrrolo[3,2,1-*hi*]indole;
- tert*-butyl (6a*S*,10a*R*)-2-(3-chloro-2-methylphenyl)-4,5,7,8,10,10a-hexahydropyrido[4,3-*b*]pyrrolo[3,2,1-*hi*]indole-9(6a*H*)-carboxylate;
- 20 (6a*S*,10a*R*)-2-(3-chloro-2-methylphenyl)-4,5,6a,7,8,9,10,10a-octahydropyrido [4,3-*b*]pyrrolo[3,2,1-*hi*]indole;
- 25 2-[(6a*S*,10a*R*)-4,5,6a,7,8,9,10,10a-octahydropyrido[4,3-*b*]pyrrolo[3,2,1-*hi*]-2-yl]-5-methoxybenzaldehyde;
- (6a*S*,10a*R*)-2-(2,6-dichlorophenyl)-4,5,6a,7,8,9,10,10a-octahydropyrido[4,3-*b*]pyrrolo[3,2,1-*hi*]indole;
- 30

N-[4-[(6a*S*,10a*R*)-4,5,6a,7,8,9,10,10a-octahydropyrido[4,3-*b*]pyrrolo[3,2,1-*hi*]indol-2-yl]-3-(trifluoromethyl)phenyl]-*N*-methylaniline;

5 4-[(6a*S*,10a*R*)-4,5,6a,7,8,9,10,10a-octahydropyrido[4,3-*b*]pyrrolo[3,2,1-*hi*]indol-2-yl]-3-(trifluoromethyl)phenylaniline;

1-(2-[(6a*S*,10a*R*)-4,5,6a,7,8,9,10,10a-octahydropyrido[4,3-*b*]pyrrolo[3,2,1-*hi*]indol-2-yl]-5-methoxyphenyl)ethanol;

10 *tert*-butyl (±)-*cis*-4,5,6,7,8a,9,10,11,12,12a-decahydroazepino[3,2,1-*hi*]pyrido[4,3-*b*]indole-11(8a*H*)-carboxylate;

tert-butyl (8a*S*,12a*R*)-2-bromo-4,5,6,7,8a,9,10,11,12,12a-decahydroazepino[3,2,1-*hi*]pyrido[4,3-*b*]indole-11(8a*H*)-carboxylate;

15 (8a*S*,12a*R*)-2-(2,4-dichlorophenyl)-4,5,6,7,8a,9,10,11,12,12a-decahydroazepino[3,2,1-*hi*]pyrido[4,3-*b*]indole;

20 (8a*S*,12a*R*)-2-(2,3-dichlorophenyl)-4,5,6,7,8a,9,10,11,12,12a-decahydroazepino[3,2,1-*hi*]pyrido[4,3-*b*]indole;

(8a*S*,12a*R*)-2-(3,4-dichlorophenyl)-4,5,6,7,8a,9,10,11,12,12a-decahydroazepino[3,2,1-*hi*]pyrido[4,3-*b*]indole;

25 (8a*S*,12a*R*)-2-(3,5-dichlorophenyl)-4,5,6,7,8a,9,10,11,12,12a-decahydroazepino[3,2,1-*hi*]pyrido[4,3-*b*]indole;

(8a*S*,12a*R*)-2-(2,5-dichlorophenyl)-4,5,6,7,8a,9,10,11,12,12a-decahydroazepino[3,2,1-*hi*]pyrido[4,3-*b*]indole;

30 (8a*S*,12a*R*)-2-(2,6-dichlorophenyl)-4,5,6,7,8a,9,10,11,12,12a-decahydroazepino[3,2,1-*hi*]pyrido[4,3-*b*]indole;

- (8a*S*,12a*R*)-2-(2-chlorophenyl)-4,5,6,7,8a,9,10,11,12,12a-decahydroazepino[3,2,1-*hi*]pyrido[4,3-*b*]indole;
- 5 (8a*S*,12a*R*)-2-(3-chlorophenyl)-4,5,6,7,8a,9,10,11,12,12a-decahydroazepino[3,2,1-*hi*]pyrido[4,3-*b*]indole;
- (8a*S*,12a*R*)-2-(4-chlorophenyl)-4,5,6,7,8a,9,10,11,12,12a-decahydroazepino[3,2,1-*hi*]pyrido[4,3-*b*]indole;
- 10 (±)-*cis*-2-(2,6-difluorophenyl)-4,5,6,7,8a,9,10,11,12,12a-decahydroazepino[3,2,1-*hi*]pyrido[4,3-*b*]indole;
- (8a*S*,12a*R*)-2-(2,6-difluorophenyl)-4,5,6,7,8a,9,10,11,12,12a-decahydroazepino[3,2,1-*hi*]pyrido[4,3-*b*]indole;
- 15 (8a*S*,12a*R*)-2-(2,3-difluorophenyl)-4,5,6,7,8a,9,10,11,12,12a-decahydroazepino[3,2,1-*hi*]pyrido[4,3-*b*]indole;
- (8a*S*,12a*R*)-2-(3,4-difluorophenyl)-4,5,6,7,8a,9,10,11,12,12a-decahydroazepino[3,2,1-*hi*]pyrido[4,3-*b*]indole;
- 20 (8a*S*,12a*R*)-2-(3-fluorophenyl)-4,5,6,7,8a,9,10,11,12,12a-decahydroazepino[3,2,1-*hi*]pyrido[4,3-*b*]indole;
- 25 (8a*S*,12a*R*)-2-[2-chloro-4-(trifluoromethyl)phenyl]-4,5,6,7,8a,9,10,11,12,12a-decahydroazepino[3,2,1-*hi*]pyrido[4,3-*b*]indole;
- (8a*S*,12a*R*)-2-(2-chloro-4-methoxyphenyl)-4,5,6,7,8a,9,10,11,12,12a-decahydroazepino[3,2,1-*hi*]pyrido[4,3-*b*]indole;
- 30

- (8a*S*,12a*R*)-2-(2-fluoro-4-methoxyphenyl)-4,5,6,7,8a,9,10,11,12,12a-decahydroazepino[3,2,1-*hi*]pyrido[4,3-*b*]indole;
- 5 (8a*S*,12a*R*)-2-(4-methoxy-2-methylphenyl)-4,5,6,7,8a,9,10,11,12,12a-decahydroazepino[3,2,1-*hi*]pyrido[4,3-*b*]indole;
- (8a*S*,12a*R*)-2-[4-methoxy-2-(trifluoromethyl)phenyl]-4,5,6,7,8a,9,10,11,12,12a-decahydroazepino[3,2,1-*hi*]pyrido[4,3-*b*]indole;
- 10 (8a*S*,12a*R*)-2-[2-(trifluoromethyl)phenyl]-4,5,6,7,8a,9,10,11,12,12a-decahydroazepino[3,2,1-*hi*]pyrido[4,3-*b*]indole;
- (8a*S*,12a*R*)-2-[4-isopropoxy-2-(trifluoromethyl)phenyl]-4,5,6,7,8a,9,10,11,12,12a-decahydroazepino[3,2,1-*hi*]pyrido[4,3-*b*]indole;
- 15 (8a*S*,12a*R*)-2-[2,4-bis(trifluoromethyl)phenyl]-4,5,6,7,8a,9,10,11,12,12a-decahydroazepino[3,2,1-*hi*]pyrido[4,3-*b*]indole;
- (8a*S*,12a*R*)-2-[4-fluoro-2-(trifluoromethyl)phenyl]-4,5,6,7,8a,9,10,11,12,12a-decahydroazepino[3,2,1-*hi*]pyrido[4,3-*b*]indole;
- 20 4-[(8a*S*,12a*R*)-4,5,6,7,8a,9,10,11,12,12a-decahydroazepino[3,2,1-*hi*]pyrido[4,3-*b*]indol-2-yl]-3-(trifluoromethyl)aniline;
- 25 4-[(8a*S*,12a*R*)-4,5,6,7,8a,9,10,11,12,12a-decahydroazepino[3,2,1-*hi*]pyrido[4,3-*b*]indol-2-yl]-*N*-methyl-3-(trifluoromethyl)aniline;
- 2-[(8a*S*,12a*R*)-4,5,6,7,8a,9,10,11,12,12a-decahydroazepino[3,2,1-*hi*]pyrido[4,3-*b*]indol-2-yl]benzaldehyde;
- 30 {2-[(8a*S*,12a*R*)-4,5,6,7,8a,9,10,11,12,12a-decahydroazepino[3,2,1-*hi*]pyrido[4,3-*b*]indol-2-yl]phenyl}methanol;

- 2-[(8a*S*,12a*R*)-4,5,6,7,8a,9,10,11,12,12a-decahydroazepino[3,2,1-*hi*]pyrido[4,3-*b*]indol-2-yl]-5-methoxybenzaldehyde;
- 5 {2-[(8a*S*,12a*R*)-4,5,6,7,8a,9,10,11,12,12a-decahydroazepino[3,2,1-*hi*]pyrido[4,3-*b*]indol-2-yl]-5-methoxyphenyl}methanol;
- 4-[(8a*S*,12a*R*)-4,5,6,7,8a,9,10,11,12,12a-decahydroazepino[3,2,1-*hi*]pyrido[4,3-*b*]indol-2-yl]-3-methylbenzonitrile;
- 10 1-{2-[(8a*S*,12a*R*)-4,5,6,7,8a,9,10,11,12,12a-decahydroazepino[3,2,1-*hi*]pyrido[4,3-*b*]indol-2-yl]-5-methoxyphenyl}ethanol;
- 15 *tert*-butyl (7a*S*,11a*R*)-2-bromo-5,6,7a,8,9,10,11,11a-octahydro-4*H*-pyrido[3',4':4,5]pyrrolo[3,2,1-*ij*]quinoline-10(7a*H*)-carboxylate;
- (7a*S*,11a*R*)-2-(2,4-dichlorophenyl)-5,6,7a,8,9,10,11,11a-octahydro-4*H*-pyrido[3',4':4,5]pyrrolo[3,2,1-*ij*]quinoline;
- 20 (7a*S*,11a*R*)-2-(3,4-dichlorophenyl)-5,6,7a,8,9,10,11,11a-octahydro-4*H*-pyrido[3',4':4,5]pyrrolo[3,2,1-*ij*]quinoline;
- (7a*S*,11a*R*)-2-(3,5-dichlorophenyl)-5,6,7a,8,9,10,11,11a-octahydro-4*H*-pyrido[3',4':4,5]pyrrolo[3,2,1-*ij*]quinoline;
- 25 (7a*S*,11a*R*)-2-(2,5-dichlorophenyl)-5,6,7a,8,9,10,11,11a-octahydro-4*H*-pyrido[3',4':4,5]pyrrolo[3,2,1-*ij*]quinoline;
- (7a*S*,11a*R*)-2-(2,6-dichlorophenyl)-5,6,7a,8,9,10,11,11a-octahydro-4*H*-pyrido[3',4':4,5]pyrrolo[3,2,1-*ij*]quinoline;
- 30

- (7a*S*,11a*R*)-2-(2-chlorophenyl)-5,6,7a,8,9,10,11,11a-octahydro-4*H*-pyrido[3',4':4,5]pyrrolo[3,2,1-*ij*]quinoline;
- 5 (7a*S*,11a*R*)-2-(3-chlorophenyl)-5,6,7a,8,9,10,11,11a-octahydro-4*H*-pyrido[3',4':4,5]pyrrolo[3,2,1-*ij*]quinoline;
- (7a*S*,11a*R*)-2-(4-chlorophenyl)-5,6,7a,8,9,10,11,11a-octahydro-4*H*-pyrido[3',4':4,5]pyrrolo[3,2,1-*ij*]quinoline;
- 10 (7a*S*,11a*R*)-2-(2,6-difluorophenyl)-5,6,7a,8,9,10,11,11a-octahydro-4*H*-pyrido[3',4':4,5]pyrrolo[3,2,1-*ij*]quinoline;
- (7a*S*,11a*R*)-2-(2,6-difluorophenyl)-10-methyl-5,6,7a,8,9,10,11,11a-octahydro-4*H*-pyrido[3',4':4,5]pyrrolo[3,2,1-*ij*]quinoline;
- 15 (7a*S*,11a*R*)-2-(2,3-difluorophenyl)-5,6,7a,8,9,10,11,11a-octahydro-4*H*-pyrido[3',4':4,5]pyrrolo[3,2,1-*ij*]quinoline;
- (7a*S*,11a*R*)-2-(3,4-difluorophenyl)-5,6,7a,8,9,10,11,11a-octahydro-4*H*-pyrido[3',4':4,5]pyrrolo[3,2,1-*ij*]quinoline;
- 20 (7a*S*,11a*R*)-2-(3-fluorophenyl)-5,6,7a,8,9,10,11,11a-octahydro-4*H*-pyrido[3',4':4,5]pyrrolo[3,2,1-*ij*]quinoline;
- (7a*S*,11a*R*)-2-[2-chloro-4-methoxyphenyl]-5,6,7a,8,9,10,11,11a-octahydro-4*H*-pyrido[3',4':4,5]pyrrolo[3,2,1-*ij*]quinoline;
- 25 (7a*S*,11a*R*)-2-[2-fluoro-4-methoxyphenyl]-5,6,7a,8,9,10,11,11a-octahydro-4*H*-pyrido[3',4':4,5]pyrrolo[3,2,1-*ij*]quinoline;
- 30 (7a*S*,11a*R*)-2-(4-methoxy-2-methylphenyl)-5,6,7a,8,9,10,11,11a-octahydro-4*H*-pyrido[3',4':4,5]pyrrolo[3,2,1-*ij*]quinoline;

- (7a*S*,11a*R*)-2-[4-methoxy-2-(trifluoromethyl)phenyl]-5,6,7a,8,9,10,11,11a-octahydro-4*H*-pyrido[3',4':4,5]pyrrolo[3,2,1-*ij*]quinoline;
- 5 4-[(7a*S*,11a*R*)-5,6,7a,8,9,10,11,11a-octahydro-4*H*-pyrido[3',4':4,5]pyrrolo[3,2,1-*ij*]quinolin-2-yl]-3-(trifluoromethyl)phenol;
- (7a*S*,11a*R*)-2-[2-(trifluoromethyl)phenyl]-5,6,7a,8,9,10,11,11a-octahydro-4*H*-pyrido[3',4':4,5]pyrrolo[3,2,1-*ij*]quinoline;
- 10 (7a*S*,11a*R*)-2-[4-isopropoxy-2-(trifluoromethyl)phenyl]-5,6,7a,8,9,10,11,11a-octahydro-4*H*-pyrido[3',4':4,5]pyrrolo[3,2,1-*ij*]quinoline;
- (7a*S*,11a*R*)-2-[2,4-bis(trifluoromethyl)phenyl]-5,6,7a,8,9,10,11,11a-octahydro-4*H*-pyrido[3',4':4,5]pyrrolo[3,2,1-*ij*]quinoline;
- 15 (7a*S*,11a*R*)-2-[4-fluoro-2-(trifluoromethyl)phenyl]-5,6,7a,8,9,10,11,11a-octahydro-4*H*-pyrido[3',4':4,5]pyrrolo[3,2,1-*ij*]quinoline;
- (7a*S*,11a*R*)-2-[4-fluoro-2-(trifluoromethyl)phenyl]-5,6,7a,8,9,10,11,11a-octahydro-4*H*-pyrido[3',4':4,5]pyrrolo[3,2,1-*ij*]quinoline;
- 20 4-[(7a*S*,11a*R*)-5,6,7a,8,9,10,11,11a-octahydro-4*H*-pyrido[3',4':4,5]pyrrolo[3,2,1-*ij*]quinolin-2-yl]-3-(trifluoromethyl)aniline;
- 4-[(7a*S*,11a*R*)-5,6,7a,8,9,10,11,11a-octahydro-4*H*-pyrido[3',4':4,5]pyrrolo[3,2,1-*ij*]quinolin-2-yl]-*N*-methyl-3-(trifluoromethyl)aniline;
- 25 (7a*S*,11a*R*)-5,6,7a,8,9,10,11,11a-octahydro-4*H*-pyrido[3',4':4,5]pyrrolo[3,2,1-*ij*]quinolin-2-yl]-3-methylbenzonitrile;
- 4-[(7a*S*,11a*R*)-5,6,7a,8,9,10,11,11a-octahydro-4*H*-pyrido[3',4':4,5]pyrrolo[3,2,1-*ij*]quinolin-2-yl]benzaldehyde;
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- {2-[(7a*S*,11a*R*)-5,6,7a,8,9,10,11,11a-octahydro-4*H*-pyrido[3',4':4,5]pyrrolo[3,2,1-*ij*]quinolin-2-yl]phenyl}methanol;
- 5 2-[(7a*S*,11a*R*)-5,6,7a,8,9,10,11,11a-octahydro-4*H*-pyrido[3',4':4,5]pyrrolo[3,2,1-*ij*]quinolin-2-yl]-5-methoxybenzaldehyde;
- {2-[(7a*S*,11a*R*)-5,6,7a,8,9,10,11,11a-octahydro-4*H*-pyrido[3',4':4,5]pyrrolo[3,2,1-*ij*]quinolin-2-yl]-5-methoxyphenyl}methanol;
- 10 (8a*S*,12a*R*)-2-[4-ethoxy-2-(trifluoromethyl)phenyl]-4,5,6,7,8a,9,10,11,12,12a-decahydroazepino[3,2,1-*hi*]pyrido[4,3*b*]indole;
- (7a*S*,11a*R*)-2-[4-ethoxy-2-(trifluoromethyl)phenyl]-5,6,7a,8,9,10,11,11a-octahydro-4*H*-pyrido[3',4':4,5]pyrrolo[3,2,1-*ij*]quinoline;
- 15 (8a*S*,12a*R*)-2-[3-chloro-2-methylphenyl]-4,5,6,7,8a,9,10,11,12,12a-decahydroazepino[3,2,1-*hi*]pyrido[4,3*b*]indole;
- (7a*S*,11a*R*)-2-[3-chloro-2-methylphenyl]-5,6,7a,8,9,10,11,11a-octahydro-4*H*-pyrido[3',4':4,5]pyrrolo[3,2,1-*ij*]quinoline;
- 20 (7a*S*,11a*R*)-2-[5-fluoro-2-methylphenyl]-5,6,7a,8,9,10,11,11a-octahydro-4*H*-pyrido[3',4':4,5]pyrrolo[3,2,1-*ij*]quinoline;
- (7a*S*,11a*R*)-2-[5-fluoro-2-methylphenyl]-5,6,7a,8,9,10,11,11a-octahydro-4*H*-pyrido[3',4':4,5]pyrrolo[3,2,1-*ij*]quinoline;
- 25 (±)-*cis*-2-(2,3-dichlorophenyl)-10-propyl-5,6,7a,8,9,10,11,11a-octahydro-4*H*-pyrido[3',4':4,5]pyrrolo[3,2,1-*ij*]quinoline ;
- (7a*S*,11a*R*)-2-(2,3-dichlorophenyl)-10-propyl-5,6,7a,8,9,10,11,11a-octahydro-4*H*-pyrido[3',4':4,5]pyrrolo[3,2,1-*ij*]quinoline ;
- 30 (±)-*cis*-10-butyl-2-(2,3-dichlorophenyl)-5,6,7a,8,9,10,11,11a-octahydro-4*H*-pyrido[3',4':4,5]pyrrolo[3,2,1-*ij*]quinoline ;

- (7a*S*,11a*R*)-10-butyl-2-(2,3-dichlorophenyl)-5,6,7a,8,9,10,11,11a-octahydro-4*H*-pyrido[3',4':4,5]pyrrolo[3,2,1-*ij*]quinoline ;
- 5 (7a*S*,11a*R*)-2-(2,3-dichlorophenyl)-10-(4-pentenyl)-5,6,7a,8,9,10,11,11a-octahydro-4*H*-pyrido[3',4':4,5]pyrrolo[3,2,1-*ij*]quinoline ;
- (7a*S*,11a*R*)-2-(2,3-dichlorophenyl)-10-(3-methyl-2-butenyl)-5,6,7a,8,9,10,11,11a-octahydro-4*H*-pyrido[3',4':4,5]pyrrolo[3,2,1-*ij*]quinoline;
- 10 (7a*S*,11a*R*)-2-(2,4-dichlorophenyl)-10-propyl-5,6,7a,8,9,10,11,11a-octahydro-4*H*-pyrido[3',4':4,5]pyrrolo[3,2,1-*ij*]quinoline ;
- (7a*S*,11a*R*)-10-butyl-2-(2,4-dichlorophenyl)-5,6,7a,8,9,10,11,11a-octahydro-4*H*-pyrido[3',4':4,5]pyrrolo[3,2,1-*ij*]quinoline ;
- 15 (7a*S*,11a*R*)-2-(2,4-dichlorophenyl)-10-(4-pentenyl)-5,6,7a,8,9,10,11,11a-octahydro-4*H*-pyrido[3',4':4,5]pyrrolo[3,2,1-*ij*]quinoline ;
- (7a*S*,11a*R*)-2-(2,4-dichlorophenyl)-10-(3-methyl-2-butenyl)-5,6,7a,8,9,10,11,11a-octahydro-4*H*-pyrido[3',4':4,5]pyrrolo[3,2,1-*ij*]quinoline;
- 20 (7a*S*,11a*R*)-10-(cyclobutylmethyl)-2-(2,3-dichlorophenyl)-5,6,7a,8,9,10,11,11a-octahydro-4*H*-pyrido[3',4':4,5]pyrrolo[3,2,1-*ij*]quinoline;
- 25 (7a*S*,11a*R*)-2-[4-methoxy-2-(trifluoromethyl)phenyl]-10-methyl-5,6,7a,8,9,10,11,11a-octahydro-4*H*-pyrido[3',4':4,5]pyrrolo[3,2,1-*ij*]quinoline;
- (7a*S*,11a*R*)-10-ethyl-2-[4-methoxy-2-(trifluoromethyl)phenyl]-5,6,7a,8,9,10,11,11a-octahydro-4*H*-pyrido[3',4':4,5]pyrrolo[3,2,1-*ij*]quinoline;
- 30

- (7a*S*,11a*R*)-2-[4-methoxy-2-(trifluoromethyl)phenyl]-10-propyl-
5,6,7a,8,9,10,11,11a-octahydro-4*H*-pyrido[3',4':4,5]pyrrolo[3,2,1-*ij*]quinoline;
- (7a*S*,11a*R*)-10-butyl-2-[4-methoxy-2-(trifluoromethyl)phenyl]-10-methyl-
5 5,6,7a,8,9,10,11,11a-octahydro-4*H*-pyrido[3',4':4,5]pyrrolo[3,2,1-*ij*]quinoline;
- (7a*S*,11a*R*)-2-[4-methoxy-2-(trifluoromethyl)phenyl]-10-(4-pentenyl)-
5,6,7a,8,9,10,11,11a-octahydro-4*H*-pyrido[3',4':4,5]pyrrolo[3,2,1-*ij*]quinoline;
- 10 (7a*S*,11a*R*)-2-[4-methoxy-2-(trifluoromethyl)phenyl]-10-(3-methyl-2-butenyl)-
5,6,7a,8,9,10,11,11a-octahydro-4*H*-pyrido[3',4':4,5]pyrrolo[3,2,1-*ij*]quinoline;
- (7a*S*,11a*R*)-10-(2-fluoroethyl)-2-[4-methoxy-2-(trifluoromethyl)phenyl]-
5,6,7a,8,9,10,11,11a-octahydro-4*H*-pyrido[3',4':4,5]pyrrolo[3,2,1-*ij*]quinoline;
15
- (7a*S*,11a*R*)-10-(2,2-difluoroethyl)-2-[4-methoxy-2-(trifluoromethyl)phenyl]-
5,6,7a,8,9,10,11,11a-octahydro-4*H*-pyrido[3',4':4,5]pyrrolo[3,2,1-*ij*]quinoline;
- (7a*S*,11a*R*)-10-(cyclobutylmethyl)-2-[4-methoxy-2-(trifluoromethyl)phenyl]-
20 5,6,7a,8,9,10,11,11a-octahydro-4*H*-pyrido[3',4':4,5]pyrrolo[3,2,1-*ij*]quinoline;
- 4-((7a*S*,11a*R*)-5,6,8,9,11,11a-hexahydro-4*H*-pyrido[3',4':4,5]pyrrolo[3,2,1-
ij]quinolin-10(7a*H*)-yl)-1-(4-fluorophenyl)-1-butanone;
- 25 4-((7a*R*,11a*S*)-5,6,8,9,11,11a-hexahydro-4*H*-pyrido[3',4':4,5]pyrrolo[3,2,1-
ij]quinolin-10(7a*H*)-yl)-1-(4-fluorophenyl)-1-butanone;
- 4-((7a*S*,11a*R*)-5,6,8,9,11,11a-hexahydro-4*H*-pyrido[3',4':4,5]pyrrolo[3,2,1-
ij]quinolin-10(7a*H*)-yl)-1-(2-aminophenyl)-1-butanone;
30
- 4-((7a*R*,11a*S*)-5,6,8,9,11,11a-hexahydro-4*H*-pyrido[3',4':4,5]pyrrolo[3,2,1-
ij]quinolin-10(7a*H*)-yl)-1-(2-aminophenyl)-1-butanone;

- (±)-*cis*-3-(5,6,8,9,11,11a-hexahydro-4*H*-pyrido[3',4':4,5]pyrrolo[3,2,1-*ij*]quinolin-10(7*aH*)-yl)propyl 4-fluorophenyl ether;
- 5 4-((±)-*cis*-5,6,8,9,11,11a-hexahydro-4*H*-pyrido[3',4':4,5]pyrrolo[3,2,1-*ij*]quinolin-10(7*aH*)-yl)-1-(4-pyridinyl)-1-butanone;
- (±)-*cis*-10-[3-(6-fluoro-1,2-benzisoxazol-3-yl)propyl]-5,6,7*a*,8,9,10,11,11*a*-octahydro-4*H*-pyrido[3',4':4,5]pyrrolo[3,2,1-*ij*]quinoline;
- 10 (7*aS*,11*aR*)-10-[3-(6-fluoro-1,2-benzisoxazol-3-yl)propyl]-5,6,7*a*,8,9,10,11,11*a*-octahydro-4*H*-pyrido[3',4':4,5]pyrrolo[3,2,1-*ij*]quinoline;
- (±)-*cis*-4-(4,5,6,7,9,10,12,12*a*-octahydroazepino[3,2,1-*hi*]pyrido[4,3-*b*]indol-11(8*aH*)-yl)-1-(4-fluorophenyl)-1-butanone;
- 15 4-((8*aS*,12*aR*)-4,5,6,7,9,10,12,12*a*-octahydroazepino[3,2,1-*hi*]pyrido[4,3-*b*]indol-11(8*aH*)-yl)-1-(4-fluorophenyl)-1-butanone;
- 20 4-((8*aR*,12*aS*)-4,5,6,7,9,10,12,12*a*-octahydroazepino[3,2,1-*hi*]pyrido[4,3-*b*]indol-11(8*aH*)-yl)-1-(4-fluorophenyl)-1-butanone;
- 4-((±)-4,5,6,7,9,10,12,12*a*-octahydroazepino[3,2,1-*hi*]pyrido[4,3-*b*]indol-11(8*aH*)-yl)-1-(2-amino-4-fluorophenyl)-1-butanone;
- 25 4-((±)-*cis*-5,6,8,9,11,11*a*-hexahydro-4*H*-pyrido[3',4':4,5]pyrrolo[3,2,1-*ij*]quinolin-10(7*aH*)-yl)-1-(2-amino-4-fluorophenyl)-1-butanone ;
- 4-((7*aS*,11*aR*)-5,6,8,9,11,11*a*-hexahydro-4*H*-pyrido[3',4':4,5]pyrrolo[3,2,1-*ij*]quinolin-10(7*aH*)-yl)-1-(2-amino-4-fluorophenyl)-1-butanone; and
- 30

4-((7a*R*,11a*S*)-5,6,8,9,11,11a-hexahydro-4*H*-pyrido[3',4':4,5]pyrrolo[3,2,1-*ij*]quinolin-10(7a*H*)-yl)-1-(2-amino-4-fluorophenyl)-1-butanone.

5 In a more preferred embodiment, the present invention provides the method as defined in Claim 1 where the compound administered is selected from the group:

4-[(±)-5,6,8,9,10,11,12,12a-octahydro-4*H*,7a*H*-azepino[4',5':4,5]pyrrolo
[3,2,1-*ij*]quinolin-10-yl]-1-(4-fluorophenyl)-1-butanone;

10

4-[(±)-5,6,8,9,10,11,12,12a-octahydro-4*H*,7a*H*-azepino[4',5':4,5]pyrrolo
[3,2,1-*ij*]quinolin-10-yl]-1-(2-amino-4-fluorophenyl)-1-butanone;

4-[(±)-4,5,6,7,9,10,11,12,13,13a-decahydro-11*H*-diazepino[4,5-*b*:3,2,1-*hi*]
indol-11-yl]-1-(4-fluorophenyl)-1-butanone;

15

4-[(±)-4,5,6,7,9,10,11,12,13,13a-decahydro-11*H*-diazepino[4,5-*b*:3,2,1-*hi*]
indol-11-yl]-1-(2-amino-4-fluorophenyl)-1-butanone;

tert-butyl (±)-*cis*-5,6,8,9,10,11,12,12a-octahydro-4*H*,7a*H*-
azepino[3',4':4,5]pyrrolo[3,2,1-*ij*]quinoline-11-carboxylate;

20

tert-butyl (±)-*cis*-2-bromo-5,6,8,9,10,11,12,12a-octahydro-4*H*,7a*H*-
azepino[3',4':4,5]pyrrolo[3,2,1-*ij*]quinoline-11-carboxylate; and

25

(±)-*cis*-2-[4-methoxy-2-(trifluoromethyl)phenyl]-5,6,8,9,10,11,12,12a-
octahydro-4*H*,7a*H*-azepino[3',4':4,5]pyrrolo[3,2,1-*ij*]quinoline.

30 In a more preferred embodiment, the present invention provides the method as defined in Claim 1 where the compound administered is selected from the group:

tert-butyl (±)-cis-2-bromo-4-oxo-4,5,6,7,9,10,12,12a-octahydroazepino[3,2,1-hi]pyrido[4,3-b]indole-11(8aH)-carboxylate;

5 tert-butyl (±)-cis-2-(2,4-dichlorophenyl)-4-oxo-4,5,6,7,9,10,12,12a-octahydroazepino[3,2,1-hi]pyrido[4,3-b]indole-11(8aH)-carboxylate;

(±)-cis-2-(2,4-dichlorophenyl)-6,7,8a,9,10,11,12,12a-octahydroazepino[3,2,1-hi]pyrido[4,3-b]indol-4(5H)-one;

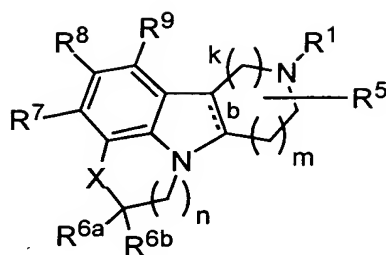
10 (8aS, 12aR)-2-(2,4-dichlorophenyl)-6,7,8a,9,10,11,12,12a-octahydroazepino[3,2,1-hi]pyrido[4,3-b]indol-4(5H)-one;

15 (8aR, 12aS)-2-(2,4-dichlorophenyl)-6,7,8a,9,10,11,12,12a-octahydroazepino[3,2,1-hi]pyrido[4,3-b]indol-4(5H)-one;

(8aS, 12aR)-2-(2,4-dichlorophenyl)-6,7,8a,9,10,11,12,12a-decahydroazepino[3,2,1-hi]pyrido[4,3-b]indol-4-ol; and

20 (8aR, 12aS)-2-(2,4-dichlorophenyl)-6,7,8a,9,10,11,12,12a-decahydroazepino[3,2,1-hi]pyrido[4,3-b]indol-4-ol.

25 Thus, in a second embodiment, the present invention provides a method for treating a human suffering from sleep disorders associated with 5HT_{2A} receptor modulation, comprising administering to a patient in need thereof a therapeutically effective amount of a compound of formula (I):



(I)

or stereoisomers or pharmaceutically acceptable salt forms thereof, wherein:

5

b is a single bond;

X is $-\text{CHR}^{10}-$ or $-\text{C}(=\text{O})-$;

10 R^1 is selected from

H,

$\text{C}(=\text{O})\text{R}^2$,

$\text{C}(=\text{O})\text{OR}^2$,

C_{1-8} alkyl,

15 C_{2-8} alkenyl,

C_{2-8} alkynyl,

C_{3-7} cycloalkyl,

C_{1-6} alkyl substituted with Z,

C_{2-6} alkenyl substituted with Z,

20 C_{2-6} alkynyl substituted with Z,

C_{3-6} cycloalkyl substituted with Z,

aryl substituted with Z,

5-6 membered heterocyclic ring system containing at least one heteroatom
selected from the group consisting of N, O, and S, said heterocyclic
ring system substituted with Z;

25

C_{1-3} alkyl substituted with Y,

- C₂₋₃ alkenyl substituted with Y,
 C₂₋₃ alkynyl substituted with Y,
 C₁₋₆ alkyl substituted with 0-2 R²,
 C₂₋₆ alkenyl substituted with 0-2 R²,
 5 C₂₋₆ alkynyl substituted with 0-2 R²,
 aryl substituted with 0-2 R², and
 5-6 membered heterocyclic ring system containing at least one heteroatom
 selected from the group consisting of N, O, and S, said heterocyclic
 ring system substituted with 0-2 R²;
 10
- Y is selected from
- C₃₋₆ cycloalkyl substituted with Z,
 aryl substituted with Z,
 5-6 membered heterocyclic ring system containing at least one heteroatom
 15 selected from the group consisting of N, O, and S, said heterocyclic
 ring system substituted with Z;
 C₃₋₆ cycloalkyl substituted with -(C₁₋₃ alkyl)-Z,
 aryl substituted with -(C₁₋₃ alkyl)-Z, and
 5-6 membered heterocyclic ring system containing at least one heteroatom
 20 selected from the group consisting of N, O, and S, said heterocyclic
 ring system substituted with -(C₁₋₃ alkyl)-Z;

- Z is selected from H,
- CH(OH)R²,
 25 -C(ethylenedioxy)R²,
 -OR²,
 -SR²,
 -NR²R³,
 -C(O)R²,

-C(O)NR²R³,
 -NR³C(O)R²,
 -C(O)OR²,
 -OC(O)R²,
 5 -CH(=NR⁴)NR²R³,
 -NHC(=NR⁴)NR²R³,
 -S(O)R²,
 -S(O)₂R²,
 -S(O)₂NR²R³, and -NR³S(O)₂R²;

10

R², at each occurrence, is independently selected from

halo,
 C₁₋₃ haloalkyl,
 C₁₋₄ alkyl,
 15 C₂₋₄ alkenyl,
 C₂₋₄ alkynyl,
 C₃₋₆ cycloalkyl,
 aryl substituted with 0-5 R⁴²;
 C₃₋₁₀ carbocyclic group substituted with 0-3 R⁴¹, and
 20 5-10 membered heterocyclic ring system containing from 1-4 heteroatoms
 selected from the group consisting of N, O, and S substituted with 0-3
 R⁴¹;

R³, at each occurrence, is independently selected from

25 H, C₁₋₄ alkyl, C₂₋₄ alkenyl, C₂₋₄ alkynyl, and
 C₁₋₄ alkoxy;

alternatively, R² and R³ join to form a 5- or 6-membered ring optionally substituted with -O- or -N(R⁴)-;

R⁴, at each occurrence, is independently selected from H and C₁₋₄ alkyl;

5

R⁵ is H or C₁₋₄ alkyl;

R^{6a} and R^{6b}, at each occurrence, are independently selected from

H, -OH, -NR⁴⁶R⁴⁷, -CF₃, C₁₋₄ alkyl, C₂₋₄ alkenyl, C₂₋₄ alkynyl, C₁₋₄
10 alkoxy, C₁₋₄ haloalkyl, C₃₋₆ cycloalkyl, and
aryl substituted with 0-3 R⁴⁴;

R⁷ and R⁹, at each occurrence, are independently selected from

H, halo, -CF₃, -OCF₃, -OH, -CN, -NO₂, -NR⁴⁶R⁴⁷,
15 C₁₋₈ alkyl, C₂₋₈ alkenyl, C₂₋₈ alkynyl, C₁₋₄ haloalkyl, C₁₋₈ alkoxy, (C₁₋₄
haloalkyl)oxy,
C₃₋₁₀ cycloalkyl substituted with 0-2 R³³,
C₁₋₄ alkyl substituted with 0-2 R¹¹,
C₃₋₁₀ carbocyclic group substituted with 0-3 R³³,
20 aryl substituted with 0-5 R³³,
5-10 membered heterocyclic ring system containing from 1-4 heteroatoms
selected from the group consisting of N, O, and S substituted with 0-3
R³¹;

25 OR¹², SR¹², NR¹²R¹³, C(O)H, C(O)R¹², C(O)NR¹²R¹³, NR¹⁴C(O)R¹²,
C(O)OR¹², OC(O)R¹², OC(O)OR¹², CH(=NR¹⁴)NR¹²R¹³,
NHC(=NR¹⁴)NR¹²R¹³, S(O)R¹², S(O)₂R¹², S(O)NR¹²R¹³,

$S(O)_2NR^{12}R^{13}$, $NR^{14}S(O)R^{12}$, $NR^{14}S(O)_2R^{12}$, $NR^{12}C(O)R^{15}$,
 $NR^{12}C(O)OR^{15}$, $NR^{12}S(O)_2R^{15}$, and $NR^{12}C(O)NHR^{15}$;

R^8 is selected from

- 5 H, halo, $-CF_3$, $-OCF_3$, $-OH$, $-CN$, $-NO_2$,
 C_{1-8} alkyl, C_{2-8} alkenyl, C_{2-8} alkynyl, C_{1-4} haloalkyl, C_{1-8} alkoxy, $(C_{1-4}$
haloalkyl)oxy,
 C_{3-10} cycloalkyl substituted with 0-2 R^{33} ,
 C_{1-4} alkyl substituted with 0-2 R^{11} ,
10 C_{2-4} alkenyl substituted with 0-2 R^{11} ,
 C_{2-4} alkynyl substituted with 0-1 R^{11} ,
 C_{3-10} carbocyclic group substituted with 0-3 R^{33} ,
aryl substituted with 0-5 R^{33} ,
5-10 membered heterocyclic ring system containing from 1-4 heteroatoms
15 selected from the group consisting of N, O, and S substituted with 0-3
 R^{31} ;
- OR^{12} , SR^{12} , $NR^{12}R^{13}$, $C(O)H$, $C(O)R^{12}$, $C(O)NR^{12}R^{13}$, $NR^{14}C(O)R^{12}$,
 $C(O)OR^{12}$, $OC(O)R^{12}$, $OC(O)OR^{12}$, $CH(=NR^{14})NR^{12}R^{13}$,
20 $NHC(=NR^{14})NR^{12}R^{13}$, $S(O)R^{12}$, $S(O)_2R^{12}$, $S(O)NR^{12}R^{13}$,
 $S(O)_2NR^{12}R^{13}$, $NR^{14}S(O)R^{12}$, $NR^{14}S(O)_2R^{12}$, $NR^{12}C(O)R^{15}$,
 $NR^{12}C(O)OR^{15}$, $NR^{12}S(O)_2R^{15}$, and $NR^{12}C(O)NHR^{15}$;

R^{10} is selected from H, $-OH$,

- 25 C_{1-6} alkyl substituted with 0-1 R^{10B} ,
 C_{2-6} alkenyl substituted with 0-1 R^{10B} ,
 C_{2-6} alkynyl substituted with 0-1 R^{10B} , and

C₁₋₆ alkoxy;

R^{10B} is selected from

C₁₋₄ alkoxy,

5 C₃₋₆ cycloalkyl,

C₃₋₁₀ carbocyclic group substituted with 0-3 R³³,

phenyl substituted with 0-3 R³³, and

5-6 membered heterocyclic ring system containing 1, 2, or 3 heteroatoms

selected from the group consisting of N, O, and S substituted with 0-2

10 R⁴⁴;

R¹¹ is selected from

H, halo, -CF₃, -CN, -NO₂,

C₁₋₈ alkyl, C₂₋₈ alkenyl, C₂₋₈ alkynyl, C₁₋₄ haloalkyl, C₁₋₈ alkoxy, C₃₋₁₀

15 cycloalkyl,

C₃₋₁₀ carbocyclic group substituted with 0-3 R³³,

aryl substituted with 0-5 R³³,

5-10 membered heterocyclic ring system containing from 1-4 heteroatoms

selected from the group consisting of N, O, and S substituted with 0-3

20 R³¹;

OR¹², SR¹², NR¹²R¹³, C(O)H, C(O)R¹², C(O)NR¹²R¹³, NR¹⁴C(O)R¹²,

C(O)OR¹², OC(O)R¹², OC(O)OR¹², CH(=NR¹⁴)NR¹²R¹³,

NHC(=NR¹⁴)NR¹²R¹³, S(O)R¹², S(O)₂R¹², S(O)NR¹²R¹³,

25 S(O)₂NR¹²R¹³, NR¹⁴S(O)R¹², NR¹⁴S(O)₂R¹², NR¹²C(O)R¹⁵,

NR¹²C(O)OR¹⁵, NR¹²S(O)₂R¹⁵, and NR¹²C(O)NHR¹⁵;

R¹², at each occurrence, is independently selected from

C₁₋₄ alkyl substituted with 0-1 R^{12a},
 C₂₋₄ alkenyl substituted with 0-1 R^{12a},
 C₂₋₄ alkynyl substituted with 0-1 R^{12a},
 C₃₋₆ cycloalkyl substituted with 0-3 R³³,
 5 phenyl substituted with 0-5 R³³;
 C₃₋₁₀ carbocyclic group substituted with 0-3 R³³, and
 5-10 membered heterocyclic ring system containing from 1-4 heteroatoms
 selected from the group consisting of N, O, and S substituted with 0-3
 R³¹;
 10 R^{12a}, at each occurrence, is independently selected from
 phenyl substituted with 0-5 R³³;
 C₃₋₁₀ carbocyclic group substituted with 0-3 R³³, and
 5-10 membered heterocyclic ring system containing from 1-4 heteroatoms
 15 selected from the group consisting of N, O, and S substituted with 0-3
 R³¹;
 R¹³, at each occurrence, is independently selected from
 H, C₁₋₄ alkyl, C₂₋₄ alkenyl, and C₂₋₄ alkynyl;
 20 alternatively, R¹² and R¹³ join to form a 5- or 6-membered ring optionally
 substituted with -O- or -N(R¹⁴)-;
 alternatively, R¹² and R¹³ when attached to N may be combined to form a 9- or 10-
 25 membered bicyclic heterocyclic ring system containing from 1-3 heteroatoms
 selected from the group consisting of N, O, and S, wherein said bicyclic
 heterocyclic ring system is unsaturated or partially saturated, wherein said
 bicyclic heterocyclic ring system is substituted with 0-3 R¹⁶;

R¹⁴, at each occurrence, is independently selected from H and C₁₋₄ alkyl;

R¹⁵, at each occurrence, is independently selected from
H, C₁₋₄ alkyl, C₂₋₄ alkenyl, and C₂₋₄ alkynyl;

5

R¹⁶, at each occurrence, is independently selected from
H, OH, halo, CN, NO₂, CF₃, SO₂R⁴⁵, NR⁴⁶R⁴⁷, -C(=O)H,
C₁₋₄ alkyl, C₂₋₄ alkenyl, C₂₋₄ alkynyl, C₁₋₄ haloalkyl,
C₁₋₃ haloalkyl-oxy-, and C₁₋₃ alkyloxy-;

10

R³¹, at each occurrence, is independently selected from
H, OH, halo, CF₃, SO₂R⁴⁵, NR⁴⁶R⁴⁷, and C₁₋₄ alkyl;

R³³, at each occurrence, is independently selected from

15 H, OH, halo, CN, NO₂, CF₃, SO₂R⁴⁵, NR⁴⁶R⁴⁷, -C(=O)H,
C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl,
C₃₋₆ cycloalkyl, C₁₋₄ haloalkyl, C₁₋₄ haloalkyl-oxy-, C₁₋₄ alkyloxy-,
C₁₋₄ alkylthio-, C₁₋₄ alkyl-C(=O)-, C₁₋₄ alkyl-C(=O)NH-, C₁₋₄ alkyl-
OC(=O)-,
20 C₁₋₄ alkyl-C(=O)O-, C₃₋₆ cycloalkyl-oxy-, C₃₋₆ cycloalkylmethyl-oxy-;
C₁₋₆ alkyl substituted with OH, methoxy, ethoxy, propoxy, or butoxy; and
C₂₋₆ alkenyl substituted with OH, methoxy, ethoxy, propoxy, or butoxy;

R⁴¹, at each occurrence, is independently selected from

25 H, CF₃, halo, OH, CO₂H, SO₂R⁴⁵, NR⁴⁶R⁴⁷, NO₂, CN, =O;
C₂₋₈ alkenyl, C₂₋₈ alkynyl, C₁₋₄ alkoxy, C₁₋₄ haloalkyl
C₁₋₄ alkyl substituted with 0-1 R⁴³,
aryl substituted with 0-3 R⁴², and

5-10 membered heterocyclic ring system containing from 1-4 heteroatoms selected from the group consisting of N, O, and S substituted with 0-3 R⁴⁴;

- 5 R⁴², at each occurrence, is independently selected from
H, CF₃, halo, OH, CO₂H, SO₂R⁴⁵, SO₂R⁴⁵, SR⁴⁵, NR⁴⁶SO₂R⁴⁵,
NR⁴⁶COR⁴⁵, NR⁴⁶R⁴⁷, NO₂, CN, CH(=NH)NH₂, NHC(=NH)NH₂,
C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₁₋₄ alkoxy, C₁₋₄ haloalkyl, C₃₋₆ cycloalkyl,
C₁₋₄ alkyl substituted with 0-1 R⁴³,
10 aryl substituted with 0-3 R⁴⁴, and
5-10 membered heterocyclic ring system containing from 1-4 heteroatoms
selected from the group consisting of N, O, and S substituted with 0-3
R⁴⁴;

- 15 R⁴³ is C₃₋₆ cycloalkyl or aryl substituted with 0-3 R⁴⁴;

R⁴⁴, at each occurrence, is independently selected from H, halo, -OH, NR⁴⁶R⁴⁷,
CO₂H, SO₂R⁴⁵, -CF₃, -OCF₃, -CN, -NO₂, C₁₋₄ alkyl, and C₁₋₄ alkoxy;

- 20 R⁴⁵ is C₁₋₄ alkyl;

R⁴⁶, at each occurrence, is independently selected from H and C₁₋₄ alkyl;

- R⁴⁷, at each occurrence, is independently selected from H, C₁₋₄ alkyl,
25 -C(=O)NH(C₁₋₄ alkyl), -SO₂(C₁₋₄ alkyl),
-C(=O)O(C₁₋₄ alkyl), -C(=O)(C₁₋₄ alkyl), and -C(=O)H;

k is 1 or 2;

m is 0, 1, or 2;

n is 0, 1, 2, or 3;

provided when m is 0 or 1 then k is 1 or 2;

provided when m is 2 then k is 1;

5

provided that when R⁶ or R^{6a} is NH₂, then X is not -CH(R¹⁰); and

provided that when n=0, then R⁶ or R^{6a} is not NH₂ or -OH.

10

In a preferred embodiment, the present invention provides the method as defined in Claim 18 where in the compound administered:

X is -CHR¹⁰- or -C(=O)-;

15

R¹ is selected from

H,

C(=O)R²,

C(=O)OR²,

20

C₁₋₈ alkyl,

C₂₋₈ alkenyl,

C₂₋₈ alkynyl,

C₃₋₇ cycloalkyl,

C₁₋₆ alkyl substituted with 0-2 R²,

25

C₂₋₆ alkenyl substituted with 0-2 R²,

C₂₋₆ alkynyl substituted with 0-2 R²,

aryl substituted with 0-2 R², and

5-6 membered heterocyclic ring system containing at least one heteroatom selected from the group consisting of N, O, and S, said heterocyclic ring system substituted with 0-2 R²;

- 5 R², at each occurrence, is independently selected from
 F, Cl, CH₂F, CHF₂, CF₃,
 C₁₋₄ alkyl,
 C₂₋₄ alkenyl,
 C₂₋₄ alkynyl,
 10 C₃₋₆ cycloalkyl,
 phenyl substituted with 0-5 R⁴²;
 C₃₋₁₀ carbocyclic group substituted with 0-3 R⁴¹, and
 5-10 membered heterocyclic ring system containing from 1-4 heteroatoms
 selected from the group consisting of N, O, and S substituted with 0-3
 15 R⁴¹;

R⁵ is H, methyl, ethyl, propyl, or butyl;

- R^{6a} is selected from
 20 H, -OH, -NR⁴⁶R⁴⁷, -CF₃,
 C₁₋₄ alkyl, C₁₋₄ alkoxy, C₁₋₄ haloalkyl, and
 aryl substituted with 0-3 R⁴⁴;

- R^{6b} is H;
 25

R⁷ and R⁹, at each occurrence, are independently selected from
 H, halo, -CF₃, -OCF₃, -OH, -CN, -NO₂, -NR⁴⁶R⁴⁷,
 C₁₋₈ alkyl, C₂₋₈ alkenyl, C₂₋₈ alkynyl, C₁₋₄ haloalkyl, C₁₋₈ alkoxy, (C₁₋₄
 haloalkyl)oxy,

- C₃₋₁₀ cycloalkyl substituted with 0-2 R³³,
 C₁₋₄ alkyl substituted with 0-2 R¹¹,
 C₃₋₁₀ carbocyclic group substituted with 0-3 R³³,
 aryl substituted with 0-5 R³³,
 5 5-10 membered heterocyclic ring system containing from 1-4 heteroatoms
 selected from the group consisting of N, O, and S substituted with 0-3
 R³¹;
- OR¹², SR¹², NR¹²R¹³, C(O)H, C(O)R¹², C(O)NR¹²R¹³, NR¹⁴C(O)R¹²,
 10 C(O)OR¹², OC(O)R¹², OC(O)OR¹², CH(=NR¹⁴)NR¹²R¹³,
 NHC(=NR¹⁴)NR¹²R¹³, S(O)R¹², S(O)₂R¹², S(O)NR¹²R¹³,
 S(O)₂NR¹²R¹³, NR¹⁴S(O)R¹², NR¹⁴S(O)₂R¹², NR¹²C(O)R¹⁵,
 NR¹²C(O)OR¹⁵, NR¹²S(O)₂R¹⁵, and NR¹²C(O)NHR¹⁵;
- 15 R⁸ is selected from
 H, halo, -CF₃, -OCF₃, -OH, -CN, -NO₂,
 C₁₋₈ alkyl, C₂₋₈ alkenyl, C₂₋₈ alkynyl, C₁₋₄ haloalkyl, C₁₋₈ alkoxy, (C₁₋₄
 haloalkyl)oxy,
 C₃₋₁₀ cycloalkyl substituted with 0-2 R³³,
 20 C₁₋₄ alkyl substituted with 0-2 R¹¹,
 C₂₋₄ alkenyl substituted with 0-2 R¹¹,
 C₂₋₄ alkynyl substituted with 0-1 R¹¹,
 C₃₋₁₀ carbocyclic group substituted with 0-3 R³³,
 aryl substituted with 0-5 R³³,
 25 5-10 membered heterocyclic ring system containing from 1-4 heteroatoms
 selected from the group consisting of N, O, and S substituted with 0-3
 R³¹;

OR¹², SR¹², NR¹²R¹³, C(O)H, C(O)R¹², C(O)NR¹²R¹³, NR¹⁴C(O)R¹²,
 C(O)OR¹², OC(O)R¹², OC(O)OR¹², CH(=NR¹⁴)NR¹²R¹³,
 NHC(=NR¹⁴)NR¹²R¹³, S(O)R¹², S(O)₂R¹², S(O)NR¹²R¹³,
 S(O)₂NR¹²R¹³, NR¹⁴S(O)R¹², NR¹⁴S(O)₂R¹², NR¹²C(O)R¹⁵,
 5 NR¹²C(O)OR¹⁵, NR¹²S(O)₂R¹⁵, and NR¹²C(O)NHR¹⁵;

R¹⁰ is selected from H, -OH,

C₁₋₆ alkyl substituted with 0-1 R^{10B},
 C₂₋₆ alkenyl substituted with 0-1 R^{10B},
 10 C₂₋₆ alkynyl substituted with 0-1 R^{10B}, and
 C₁₋₆ alkoxy;

R^{10B} is selected from

C₁₋₄ alkoxy,
 15 C₃₋₆ cycloalkyl,
 C₃₋₁₀ carbocyclic group substituted with 0-3 R³³,
 phenyl substituted with 0-3 R³³, and
 5-6 membered heterocyclic ring system containing 1, 2, or 3 heteroatoms
 selected from the group consisting of N, O, and S substituted with 0-2
 20 R⁴⁴;

R¹¹ is selected from

H, halo, -CF₃, -CN, -NO₂,
 C₁₋₈ alkyl, C₂₋₈ alkenyl, C₂₋₈ alkynyl, C₁₋₄ haloalkyl, C₁₋₈ alkoxy, C₃₋₁₀
 25 cycloalkyl,
 C₃₋₁₀ carbocyclic group substituted with 0-3 R³³,
 aryl substituted with 0-5 R³³,

5-10 membered heterocyclic ring system containing from 1-4 heteroatoms
selected from the group consisting of N, O, and S substituted with 0-3
R³¹;

5 OR¹², SR¹², NR¹²R¹³, C(O)H, C(O)R¹², C(O)NR¹²R¹³, NR¹⁴C(O)R¹²,
C(O)OR¹², OC(O)R¹², OC(O)OR¹², CH(=NR¹⁴)NR¹²R¹³,
NHC(=NR¹⁴)NR¹²R¹³, S(O)R¹², S(O)₂R¹², S(O)NR¹²R¹³,
S(O)₂NR¹²R¹³, NR¹⁴S(O)R¹², NR¹⁴S(O)₂R¹², NR¹²C(O)R¹⁵,
NR¹²C(O)OR¹⁵, NR¹²S(O)₂R¹⁵, and NR¹²C(O)NHR¹⁵;

10

R¹², at each occurrence, is independently selected from

C₁₋₄ alkyl substituted with 0-1 R^{12a},

C₂₋₄ alkenyl substituted with 0-1 R^{12a},

C₂₋₄ alkynyl substituted with 0-1 R^{12a},

15 C₃₋₆ cycloalkyl substituted with 0-3 R³³,

phenyl substituted with 0-5 R³³;

C₃₋₁₀ carbocyclic group substituted with 0-3 R³³, and

5-10 membered heterocyclic ring system containing from 1-4 heteroatoms
selected from the group consisting of N, O, and S substituted with 0-3
20 R³¹;

R^{12a}, at each occurrence, is independently selected from

phenyl substituted with 0-5 R³³;

C₃₋₁₀ carbocyclic group substituted with 0-3 R³³, and

25 5-10 membered heterocyclic ring system containing from 1-4 heteroatoms
selected from the group consisting of N, O, and S substituted with 0-3
R³¹;

R¹³, at each occurrence, is independently selected from

H, C₁₋₄ alkyl, C₂₋₄ alkenyl, and C₂₋₄ alkynyl;

alternatively, R¹² and R¹³ join to form a 5- or 6-membered ring optionally

5 substituted with -O- or -N(R¹⁴)-;

alternatively, R¹² and R¹³ when attached to N may be combined to form a 9- or 10-
membered bicyclic heterocyclic ring system containing from 1-3 heteroatoms
selected from the group consisting of N, O, and S, wherein said bicyclic
10 heterocyclic ring system is unsaturated or partially saturated, wherein said
bicyclic heterocyclic ring system is substituted with 0-3 R¹⁶;

R¹⁴, at each occurrence, is independently selected from H and C₁₋₄ alkyl;

15 R¹⁵, at each occurrence, is independently selected from

H, C₁₋₄ alkyl, C₂₋₄ alkenyl, and C₂₋₄ alkynyl;

R¹⁶, at each occurrence, is independently selected from

20 H, OH, halo, CN, NO₂, CF₃, SO₂R⁴⁵, NR⁴⁶R⁴⁷, -C(=O)H,
C₁₋₄ alkyl, C₂₋₄ alkenyl, C₂₋₄ alkynyl, C₁₋₄ haloalkyl,
C₁₋₃ haloalkyl-oxy-, and C₁₋₃ alkyloxy-;

R³¹, at each occurrence, is independently selected from

25 H, OH, halo, CF₃, SO₂R⁴⁵, NR⁴⁶R⁴⁷, and C₁₋₄ alkyl;

R³³, at each occurrence, is independently selected from

H, OH, halo, CN, NO₂, CF₃, SO₂R⁴⁵, NR⁴⁶R⁴⁷, -C(=O)H,
C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl,
C₃₋₆ cycloalkyl, C₁₋₄ haloalkyl, C₁₋₄ haloalkyl-oxy-, C₁₋₄ alkyloxy-,

C₁₋₄ alkylthio-, C₁₋₄ alkyl-C(=O)-, C₁₋₄ alkyl-C(=O)NH-, C₁₋₄ alkyl-
 OC(=O)-,
 C₁₋₄ alkyl-C(=O)O-, C₃₋₆ cycloalkyl-oxy-, C₃₋₆ cycloalkylmethyl-oxy-;
 C₁₋₆ alkyl substituted with OH, methoxy, ethoxy, propoxy, or butoxy; and
 5 C₂₋₆ alkenyl substituted with OH, methoxy, ethoxy, propoxy, or butoxy;

R⁴¹, at each occurrence, is independently selected from

H, CF₃, halo, OH, CO₂H, SO₂R⁴⁵, NR⁴⁶R⁴⁷, NO₂, CN;
 C₂₋₈ alkenyl, C₂₋₈ alkynyl, C₁₋₄ alkoxy, C₁₋₄ haloalkyl
 10 C₁₋₄ alkyl substituted with 0-1 R⁴³,
 aryl substituted with 0-3 R⁴², and
 5-10 membered heterocyclic ring system containing from 1-4 heteroatoms
 selected from the group consisting of N, O, and S substituted with 0-3
 R⁴⁴;

15

R⁴², at each occurrence, is independently selected from

H, CF₃, halo, OH, CO₂H, SO₂R⁴⁵, NR⁴⁶R⁴⁷, NO₂, CN, CH(=NH)NH₂,
 NHC(=NH)NH₂,
 C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₁₋₄ alkoxy, C₁₋₄ haloalkyl, C₃₋₆ cycloalkyl,
 20 C₁₋₄ alkyl substituted with 0-1 R⁴³,
 aryl substituted with 0-3 R⁴⁴, and
 5-10 membered heterocyclic ring system containing from 1-4 heteroatoms
 selected from the group consisting of N, O, and S substituted with 0-3
 R⁴⁴;

25

R⁴³ is C₃₋₆ cycloalkyl or aryl substituted with 0-3 R⁴⁴;

R⁴⁴, at each occurrence, is independently selected from H, halo, -OH, NR⁴⁶R⁴⁷,
 CO₂H, SO₂R⁴⁵, -CF₃, -OCF₃, -CN, -NO₂, C₁₋₄ alkyl, and C₁₋₄ alkoxy;

R⁴⁵ is C₁₋₄ alkyl;

R⁴⁶, at each occurrence, is independently selected from H and C₁₋₄ alkyl;

5

R⁴⁷, at each occurrence, is independently selected from H and C₁₋₄ alkyl;

k is 1 or 2;

m is 0, 1, or 2; and

10 n is 0, 1, 2, or 3.

In a more preferred embodiment, the present invention provides the method as defined in Claim 19 where in the compound administered:

15

X is -CHR¹⁰-;

R¹ is selected from

H,

20 C(=O)R²,

C(=O)OR²,

C₁₋₆ alkyl,

C₂₋₆ alkenyl,

C₂₋₆ alkynyl,

25 C₃₋₆ cycloalkyl,

C₁₋₄ alkyl substituted with 0-2 R²,

C₂₋₄ alkenyl substituted with 0-2 R², and

C₂₋₄ alkynyl substituted with 0-2 R²;

R², at each occurrence, is independently selected from

- C₁₋₄ alkyl,
- C₂₋₄ alkenyl,
- C₂₋₄ alkynyl,
- 5 C₃₋₆ cycloalkyl,
- phenyl substituted with 0-5 R⁴²;
- C₃₋₁₀ carbocyclic group substituted with 0-3 R⁴¹, and
- 5-10 membered heterocyclic ring system containing from 1-4 heteroatoms
- selected from the group consisting of N, O, and S substituted with 0-3
- 10 R⁴¹;

R⁵ is H, methyl, ethyl, propyl, or butyl;

R^{6a} is selected independently from

- 15 H, -OH, -NR⁴⁶R⁴⁷, -CF₃, C₁₋₃ alkyl, and C₁₋₃ alkoxy;

R^{6b} is H;

R⁷ and R⁹, at each occurrence, are independently selected from

- 20 H, halo, -CF₃, -OCF₃, -OH, -CN, -NO₂, -NR⁴⁶R⁴⁷,
- C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₁₋₆ haloalkyl, C₁₋₆ alkoxy, (C₁₋₄
- haloalkyl)oxy,
- C₃₋₁₀ cycloalkyl substituted with 0-2 R³³,
- C₁₋₄ alkyl substituted with 0-2 R¹¹,
- 25 C₃₋₁₀ carbocyclic group substituted with 0-3 R³³,
- aryl substituted with 0-5 R³³,

5-10 membered heterocyclic ring system containing from 1-4 heteroatoms
selected from the group consisting of N, O, and S substituted with 0-3
R³¹;

5 OR¹², SR¹², NR¹²R¹³, C(O)H, C(O)R¹², C(O)NR¹²R¹³, NR¹⁴C(O)R¹²,
C(O)OR¹², OC(O)R¹², OC(O)OR¹², CH(=NR¹⁴)NR¹²R¹³,
NHC(=NR¹⁴)NR¹²R¹³, S(O)R¹², S(O)₂R¹², S(O)NR¹²R¹³,
S(O)₂NR¹²R¹³, NR¹⁴S(O)R¹², and NR¹⁴S(O)₂R¹²;

10 R⁸ is selected from

H, halo, -CF₃, -OCF₃, -OH, -CN, -NO₂,

C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₁₋₆ haloalkyl, C₁₋₆ alkoxy, (C₁₋₄
haloalkyl)oxy,

C₃₋₁₀ cycloalkyl substituted with 0-2 R³³,

15 C₁₋₄ alkyl substituted with 0-2 R¹¹,

C₂₋₄ alkenyl substituted with 0-2 R¹¹,

C₂₋₄ alkynyl substituted with 0-1 R¹¹,

C₃₋₁₀ carbocyclic group substituted with 0-3 R³³,

aryl substituted with 0-5 R³³,

20 5-10 membered heterocyclic ring system containing from 1-4 heteroatoms
selected from the group consisting of N, O, and S substituted with 0-3
R³¹;

25 OR¹², SR¹², NR¹²R¹³, C(O)H, C(O)R¹², C(O)NR¹²R¹³, NR¹⁴C(O)R¹²,
C(O)OR¹², OC(O)R¹², OC(O)OR¹², CH(=NR¹⁴)NR¹²R¹³,
NHC(=NR¹⁴)NR¹²R¹³, S(O)R¹², S(O)₂R¹², S(O)NR¹²R¹³,
S(O)₂NR¹²R¹³, NR¹⁴S(O)R¹², NR¹⁴S(O)₂R¹², NR¹²C(O)R¹⁵,
NR¹²C(O)OR¹⁵, NR¹²S(O)₂R¹⁵, and NR¹²C(O)NHR¹⁵;

R¹⁰ is selected from H, -OH,

C₁₋₆ alkyl substituted with 0-1 R^{10B},

C₂₋₆ alkenyl substituted with 0-1 R^{10B},

5 C₂₋₆ alkynyl substituted with 0-1 R^{10B}, and

C₁₋₆ alkoxy;

R^{10B} is selected from

C₁₋₄ alkoxy,

10 C₃₋₆ cycloalkyl,

C₃₋₁₀ carbocyclic group substituted with 0-3 R³³,

phenyl substituted with 0-3 R³³, and

5-6 membered heterocyclic ring system containing 1, 2, or 3 heteroatoms

selected from the group consisting of N, O, and S substituted with 0-2

15 R⁴⁴;

R¹¹ is selected from

H, halo, -CF₃, -CN, -NO₂, C₁₋₆ alkyl,

C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₁₋₄ haloalkyl, C₁₋₆ alkoxy, C₃₋₁₀ cycloalkyl,

20 C₃₋₁₀ carbocyclic group substituted with 0-3 R³³,

aryl substituted with 0-5 R³³,

5-10 membered heterocyclic ring system containing from 1-4 heteroatoms

selected from the group consisting of N, O, and S substituted with 0-3

R³¹;

25

OR¹², SR¹², NR¹²R¹³, C(O)H, C(O)R¹², C(O)NR¹²R¹³, NR¹⁴C(O)R¹²,

C(O)OR¹², OC(O)R¹², OC(O)OR¹², CH(=NR¹⁴)NR¹²R¹³,

$\text{NHC(=NR}^{14})\text{NR}^{12}\text{R}^{13}$, S(O)R^{12} , $\text{S(O)}_2\text{R}^{12}$, $\text{S(O)NR}^{12}\text{R}^{13}$,
 $\text{S(O)}_2\text{NR}^{12}\text{R}^{13}$, $\text{NR}^{14}\text{S(O)R}^{12}$, and $\text{NR}^{14}\text{S(O)}_2\text{R}^{12}$;

R^{12} , at each occurrence, is independently selected from

- 5 C_{1-4} alkyl substituted with 0-1 R^{12a} ,
- C_{2-4} alkenyl substituted with 0-1 R^{12a} ,
- C_{2-4} alkynyl substituted with 0-1 R^{12a} ,
- C_{3-6} cycloalkyl substituted with 0-3 R^{33} ,
- phenyl substituted with 0-5 R^{33} ;
- 10 C_{3-10} carbocyclic group substituted with 0-3 R^{33} , and
- 5-10 membered heterocyclic ring system containing from 1-4 heteroatoms
 selected from the group consisting of N, O, and S substituted with 0-3
 R^{31} ;
- 15 R^{12a} , at each occurrence, is independently selected from
- phenyl substituted with 0-5 R^{33} ;
- C_{3-10} carbocyclic group substituted with 0-3 R^{33} , and
- 5-10 membered heterocyclic ring system containing from 1-4 heteroatoms
 selected from the group consisting of N, O, and S substituted with 0-3
- 20 R^{31} ;

R^{13} , at each occurrence, is independently selected from

- H, C_{1-4} alkyl, C_{2-4} alkenyl, and C_{2-4} alkynyl;
- 25 alternatively, R^{12} and R^{13} join to form a 5- or 6-membered ring optionally
 substituted with -O- or - $\text{N(R}^{14})$ -;

- alternatively, R¹² and R¹³ when attached to N may be combined to form a 9- or 10-membered bicyclic heterocyclic ring system containing from 1-3 heteroatoms selected from the group consisting of N, O, and S, wherein said bicyclic heterocyclic ring system is unsaturated or partially saturated, wherein said
- 5 bicyclic heterocyclic ring system is substituted with 0-3 R¹⁶;
- R¹⁴, at each occurrence, is independently selected from H, methyl, ethyl, propyl, and butyl;
- 10 R¹⁵, at each occurrence, is independently selected from H, C₁₋₄ alkyl, C₂₋₄ alkenyl, and C₂₋₄ alkynyl;
- R¹⁶, at each occurrence, is independently selected from H, OH, F, Cl, CN, NO₂, CF₃, SO₂R⁴⁵, NR⁴⁶R⁴⁷, -C(=O)H,
- 15 methyl, ethyl, methoxy, ethoxy, trifluoromethyl, and trifluoromethoxy;
- R³¹, at each occurrence, is independently selected from H, OH, halo, CF₃, SO₂R⁴⁵, NR⁴⁶R⁴⁷, and C₁₋₄ alkyl;
- 20 R³³, at each occurrence, is independently selected from H, OH, halo, CN, NO₂, CF₃, SO₂R⁴⁵, NR⁴⁶R⁴⁷, -C(=O)H, C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₃₋₆ cycloalkyl, C₁₋₄ haloalkyl, C₁₋₄ haloalkyl-oxy-, C₁₋₄ alkyloxy-, C₁₋₄ alkylthio-, C₁₋₄ alkyl-C(=O)-, C₁₋₄ alkyl-C(=O)NH-, C₁₋₄ alkyl-
- 25 OC(=O)-, C₁₋₄ alkyl-C(=O)O-, C₃₋₆ cycloalkyl-oxy-, C₃₋₆ cycloalkylmethyl-oxy-, C₁₋₆ alkyl substituted with OH, methoxy, ethoxy, propoxy, or butoxy; and C₂₋₆ alkenyl substituted with OH, methoxy, ethoxy, propoxy, or butoxy;

- R⁴¹, at each occurrence, is independently selected from
H, CF₃, halo, OH, CO₂H, SO₂R⁴⁵, NR⁴⁶R⁴⁷, NO₂, CN,
C₂₋₈ alkenyl, C₂₋₈ alkynyl, C₁₋₄ alkoxy, C₁₋₄ haloalkyl
C₁₋₄ alkyl substituted with 0-1 R⁴³,
5 aryl substituted with 0-3 R⁴², and
5-10 membered heterocyclic ring system containing from 1-4 heteroatoms
selected from the group consisting of N, O, and S substituted with 0-3
R⁴⁴;
- 10 R⁴², at each occurrence, is independently selected from
H, CF₃, halo, OH, CO₂H, SO₂R⁴⁵, NR⁴⁶R⁴⁷, NO₂, CN, CH(=NH)NH₂,
NHC(=NH)NH₂,
C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₁₋₄ alkoxy, C₁₋₄ haloalkyl, C₃₋₆ cycloalkyl,
C₁₋₄ alkyl substituted with 0-1 R⁴³,
15 aryl substituted with 0-3 R⁴⁴, and
5-10 membered heterocyclic ring system containing from 1-4 heteroatoms
selected from the group consisting of N, O, and S substituted with 0-3
R⁴⁴;
- 20 R⁴³ is C₃₋₆ cycloalkyl or aryl substituted with 0-3 R⁴⁴;
- R⁴⁴, at each occurrence, is independently selected from H, halo, -OH, NR⁴⁶R⁴⁷,
CO₂H, SO₂R⁴⁵, -CF₃, -OCF₃, -CN, -NO₂, C₁₋₄ alkyl, and C₁₋₄ alkoxy;
- 25 R⁴⁵ is C₁₋₄ alkyl;

R⁴⁶, at each occurrence, is independently selected from H and C₁₋₄ alkyl;

R⁴⁷, at each occurrence, is independently selected from H and C₁₋₄ alkyl;

k is 1 or 2;

m is 0 or 1; and

5 n is 0, 1 or 2.

In a more preferred embodiment, the present invention provides the method as defined in Claim 19 where in the compound administered:

10

X is -CH₂-;

R¹ is selected from

- 15 H,
C₁₋₄ alkyl,
C₂₋₄ alkenyl,
C₂₋₄ alkynyl,
C₃₋₄ cycloalkyl,
C₁₋₃ alkyl substituted with 0-1 R²,
20 C₂₋₃ alkenyl substituted with 0-1 R², and
C₂₋₃ alkynyl substituted with 0-1 R²;

R², at each occurrence, is independently selected from

- 25 C₁₋₄ alkyl,
C₂₋₄ alkenyl,
C₂₋₄ alkynyl,
C₃₋₆ cycloalkyl,
phenyl substituted with 0-5 R⁴²;
C₃₋₆ carbocyclic group substituted with 0-3 R⁴¹, and

5-6 membered heterocyclic ring system containing 1, 2, or 3 heteroatoms
selected from the group consisting of N, O, and S substituted with 0-3
R⁴¹;

5 R⁵ is H, methyl, ethyl, propyl, or butyl;

R^{6a} is H, methyl, ethyl, methoxy, -OH, or -CF₃;

R^{6b} is H;

10

R⁷ and R⁹, at each occurrence, are independently selected from

H, halo, -CF₃, -OCF₃, -OH, -CN, -NO₂, -NR⁴⁶R⁴⁷,

C₁₋₄ alkyl, C₂₋₄ alkenyl, C₂₋₄ alkynyl, C₁₋₄ haloalkyl, C₁₋₄ alkoxy, (C₁₋₄
haloalkyl)oxy,

15

C₃₋₁₀ cycloalkyl substituted with 0-2 R³³,

C₁₋₄ alkyl substituted with 0-2 R¹¹,

C₃₋₁₀ carbocyclic group substituted with 0-3 R³³,

aryl substituted with 0-5 R³³, and

5-6 membered heterocyclic ring system containing 1, 2, or 3 heteroatoms

20

selected from the group consisting of N, O, and S substituted with 0-3
R³¹;

R⁸ is selected from

H, halo, -CF₃, -OCF₃, -OH, -CN, -NO₂,

25

C₁₋₄ alkyl, C₂₋₄ alkenyl, C₂₋₄ alkynyl, C₁₋₄ haloalkyl, C₁₋₄ alkoxy, (C₁₋₄
haloalkyl)oxy,

C₃₋₁₀ cycloalkyl substituted with 0-2 R³³,

C₁₋₄ alkyl substituted with 0-2 R¹¹,

- C₂₋₄ alkenyl substituted with 0-2 R¹¹,
 C₂₋₄ alkynyl substituted with 0-1 R¹¹,
 C₃₋₁₀ carbocyclic group substituted with 0-3 R³³,
 aryl substituted with 0-5 R³³,
 5 5-6 membered heterocyclic ring system containing 1, 2, or 3 heteroatoms
 selected from the group consisting of N, O, and S substituted with 0-3
 R³¹;
 OR¹², SR¹², NR¹²R¹³, NR¹²C(O)R¹⁵, NR¹²C(O)OR¹⁵, NR¹²S(O)₂R¹⁵,
 and NR¹²C(O)NHR¹⁵;
 10
 R¹¹ is selected from
 H, halo, -CF₃, -CN, -NO₂,
 C₁₋₄ alkyl, C₂₋₄ alkenyl, C₂₋₄ alkynyl, C₁₋₄ haloalkyl, C₁₋₄ alkoxy, (C₁₋₄
 haloalkyl)oxy,
 15 C₃₋₁₀ cycloalkyl substituted with 0-2 R³³,
 C₃₋₁₀ carbocyclic group substituted with 0-3 R³³,
 aryl substituted with 0-5 R³³, and
 5-6 membered heterocyclic ring system containing 1, 2, or 3 heteroatoms
 selected from the group consisting of N, O, and S substituted with 0-3
 20 R³¹;

- R¹², at each occurrence, is independently selected from
 C₁₋₄ alkyl substituted with 0-1 R^{12a},
 C₂₋₄ alkenyl substituted with 0-1 R^{12a},
 25 C₂₋₄ alkynyl substituted with 0-1 R^{12a},
 C₃₋₆ cycloalkyl substituted with 0-3 R³³,
 phenyl substituted with 0-5 R³³,
 C₃₋₁₀ carbocyclic group substituted with 0-3 R³³, and

5-10 membered heterocyclic ring system containing from 1-4 heteroatoms selected from the group consisting of N, O, and S substituted with 0-3 R³¹;

5 R^{12a}, at each occurrence, is independently selected from
phenyl substituted with 0-5 R³³;
C₃-10 carbocyclic group substituted with 0-3 R³³, and
5-10 membered heterocyclic ring system containing from 1-4 heteroatoms
selected from the group consisting of N, O, and S substituted with 0-3
10 R³¹;

R¹³, at each occurrence, is independently selected from
H, C₁₋₄ alkyl, C₂₋₄ alkenyl, and C₂₋₄ alkynyl;

15 alternatively, R¹² and R¹³ join to form a 5- or 6-membered ring optionally
substituted with -O- or -N(R¹⁴)-;

alternatively, R¹² and R¹³ when attached to N may be combined to form a 9- or 10-
membered bicyclic heterocyclic ring system containing from 1-3 heteroatoms
20 selected from the group consisting of one N, two N, three N, one N one O, and
one N one S; wherein said bicyclic heterocyclic ring system is unsaturated or
partially saturated, wherein said bicyclic heterocyclic ring system is substituted
with 0-2 R¹⁶;

25 R¹⁴, at each occurrence, is independently selected from H, methyl, ethyl, propyl, and
butyl;

R¹⁵, at each occurrence, is independently selected from H, methyl, ethyl, propyl, and
butyl;

30

R¹⁶, at each occurrence, is independently selected from

H, OH, F, Cl, CN, NO₂, methyl, ethyl, methoxy, ethoxy, trifluoromethyl, and trifluoromethoxy;

5 R³¹, at each occurrence, is independently selected from

H, OH, halo, CF₃, methyl, ethyl, and propyl;

R³³, at each occurrence, is independently selected from

10 H, OH, halo, CN, NO₂, CF₃, SO₂R⁴⁵, NR⁴⁶R⁴⁷, -C(=O)H,
C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl,
C₃₋₆ cycloalkyl, C₁₋₄ haloalkyl, C₁₋₄ haloalkyl-oxy-, C₁₋₄ alkyloxy-,
C₁₋₄ alkylthio-, C₁₋₄ alkyl-C(=O)-, C₁₋₄ alkyl-C(=O)NH-, C₁₋₄ alkyl-
OC(=O)-,
C₁₋₄ alkyl-C(=O)O-, C₃₋₆ cycloalkyl-oxy-, C₃₋₆ cycloalkylmethyl-oxy-;
15 C₁₋₆ alkyl substituted with OH, methoxy, ethoxy, propoxy, or butoxy; and
C₂₋₆ alkenyl substituted with OH, methoxy, ethoxy, propoxy, or butoxy;

R⁴¹, at each occurrence, is independently selected from

20 H, CF₃, halo, OH, CO₂H, SO₂R⁴⁵, NR⁴⁶R⁴⁷, NO₂, CN,
C₂₋₄ alkenyl, C₂₋₄ alkynyl, C₁₋₃ alkoxy, C₁₋₃ haloalkyl, and C₁₋₃ alkyl;

R⁴², at each occurrence, is independently selected from

25 H, CF₃, halo, OH, CO₂H, SO₂R⁴⁵, NR⁴⁶R⁴⁷, NO₂, CN, CH(=NH)NH₂,
NHC(=NH)NH₂,
C₂₋₄ alkenyl, C₂₋₄ alkynyl, C₁₋₃ alkoxy, C₁₋₃ haloalkyl, C₃₋₆ cycloalkyl, and
C₁₋₃ alkyl;

R⁴³ is cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, phenyl, or pyridyl, each substituted with 0-3 R⁴⁴;

R⁴⁴, at each occurrence, is independently selected from H, halo, -OH, NR⁴⁶R⁴⁷,
CO₂H, SO₂R⁴⁵, -CF₃, -OCF₃, -CN, -NO₂, methyl, ethyl, propyl, butyl,
methoxy, ethoxy, propoxy, and butoxy;

5

R⁴⁵ is methyl, ethyl, propyl, or butyl;

R⁴⁶, at each occurrence, is independently selected from H, methyl, ethyl, propyl, and
butyl;

10

R⁴⁷, at each occurrence, is independently selected from from H, methyl, ethyl, propyl,
and butyl;

k is 1;

15

m is 1; and

n is 0, 1 or 2.

In a more preferred embodiment, the present invention provides the method as
20 defined in Claim 19 where in the compound administered:

X is -CH₂-;

R¹ is selected from

25

H,

C₁₋₄ alkyl,

C₂₋₄ alkenyl,

C₂₋₄ alkynyl,

C₃₋₄ cycloalkyl,

30

C₁₋₃ alkyl substituted with 0-1 R²,

C₂₋₃ alkenyl substituted with 0-1 R², and

C₂₋₃ alkynyl substituted with 0-1 R²;

R², at each occurrence, is independently selected from

5 C₁₋₄ alkyl,

C₂₋₄ alkenyl,

C₂₋₄ alkynyl,

C₃₋₆ cycloalkyl,

phenyl substituted with 0-5 R⁴²;

10 C₃₋₆ carbocyclic group substituted with 0-3 R⁴¹, and

5-6 membered heterocyclic ring system containing 1, 2, or 3 heteroatoms

selected from the group consisting of N, O, and S substituted with 0-3

R⁴¹;

15 R⁵ is H, methyl, ethyl, propyl, or butyl;

R^{6a} is H, methyl, ethyl, methoxy, -OH, or -CF₃;

R^{6b} is H;

20

R⁷ and R⁹, at each occurrence, are independently selected from

H, F, Cl, -CH₃, -OCH₃, -CF₃, -OCF₃, -CN, and -NO₂,

R⁸ is selected from

25 H, F, Cl, Br, -CF₃, -OCF₃, -OH, -CN, -NO₂,

C₁₋₄ alkyl, C₂₋₄ alkenyl, C₂₋₄ alkynyl, C₁₋₄ haloalkyl, C₁₋₄ alkoxy, (C₁₋₄
haloalkyl)oxy,

C₃₋₁₀ cycloalkyl substituted with 0-2 R³³,

C₁₋₄ alkyl substituted with 0-2 R¹¹,

- C₂₋₄ alkenyl substituted with 0-2 R¹¹,
 C₂₋₄ alkynyl substituted with 0-1 R¹¹,
 C₃₋₁₀ carbocyclic group substituted with 0-3 R³³,
 aryl substituted with 0-5 R³³,
 5 5-6 membered heterocyclic ring system containing 1, 2, or 3 heteroatoms
 selected from the group consisting of N, O, and S substituted with 0-3
 R³¹;
 OR¹², SR¹², NR¹²R¹³, NR¹²C(O)R¹⁵, NR¹²C(O)OR¹⁵, NR¹²S(O)₂R¹⁵,
 and NR¹²C(O)NHR¹⁵;
 10
 R¹¹ is selected from
 H, halo, -CF₃, -CN, -NO₂,
 C₁₋₄ alkyl, C₂₋₄ alkenyl, C₂₋₄ alkynyl, C₁₋₄ haloalkyl, C₁₋₄ alkoxy, (C₁₋₄
 haloalkyl)oxy,
 15 C₃₋₁₀ cycloalkyl substituted with 0-2 R³³,
 C₃₋₁₀ carbocyclic group substituted with 0-3 R³³,
 aryl substituted with 0-5 R³³, and
 5-6 membered heterocyclic ring system containing 1, 2, or 3 heteroatoms
 selected from the group consisting of N, O, and S substituted with 0-3
 20 R³¹;

- R¹², at each occurrence, is independently selected from
 C₁₋₄ alkyl substituted with 0-1 R^{12a},
 C₂₋₄ alkenyl substituted with 0-1 R^{12a},
 25 C₂₋₄ alkynyl substituted with 0-1 R^{12a},
 C₃₋₆ cycloalkyl substituted with 0-3 R³³,
 phenyl substituted with 0-5 R³³;
 C₃₋₁₀ carbocyclic group substituted with 0-3 R³³, and

5-10 membered heterocyclic ring system containing from 1-4 heteroatoms
selected from the group consisting of N, O, and S substituted with 0-3
R³¹;

5 R^{12a}, at each occurrence, is independently selected from
phenyl substituted with 0-5 R³³;
C₃-10 carbocyclic group substituted with 0-3 R³³, and
5-10 membered heterocyclic ring system containing from 1-4 heteroatoms
selected from the group consisting of N, O, and S substituted with 0-3
10 R³¹;

R¹³, at each occurrence, is independently selected from
H, C₁₋₄ alkyl, C₂₋₄ alkenyl, and C₂₋₄ alkynyl;

15 alternatively, R¹² and R¹³ join to form a 5- or 6-membered ring optionally
substituted with -O- or -N(R¹⁴)-;

alternatively, R¹² and R¹³ when attached to N may be combined to form a 9- or 10-
membered bicyclic heterocyclic ring system containing from 1-3 heteroatoms
20 selected from the group consisting of N, O, and S; wherein said bicyclic
heterocyclic ring system is selected from indolyl, indolinyl, indazolyl,
benzimidazolyl, benzimidazoliny, benzotriazolyl, benzoxazolyl,
benzoxazoliny, benzthiazolyl, and dioxobenzthiazolyl; wherein said bicyclic
heterocyclic ring system is substituted with 0-1 R¹⁶;

25 R¹⁴, at each occurrence, is independently selected from H, methyl, ethyl, propyl, and
butyl;

R¹⁵, at each occurrence, is independently selected from H, methyl, ethyl, propyl, and
30 butyl;

R¹⁶, at each occurrence, is independently selected from

H, OH, F, Cl, CN, NO₂, methyl, ethyl, methoxy, ethoxy, trifluoromethyl, and trifluoromethoxy;

5

R³¹, at each occurrence, is independently selected from

H, OH, halo, CF₃, methyl, ethyl, and propyl;

R³³, at each occurrence, is independently selected from

10 H, OH, halo, CN, NO₂, CF₃, SO₂R⁴⁵, NR⁴⁶R⁴⁷, -C(=O)H,
C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl,
C₃₋₆ cycloalkyl, C₁₋₄ haloalkyl, C₁₋₄ haloalkyl-oxy-, C₁₋₄ alkyloxy-,
C₁₋₄ alkylthio-, C₁₋₄ alkyl-C(=O)-, C₁₋₄ alkyl-C(=O)NH-, C₁₋₄ alkyl-
OC(=O)-,
15 C₁₋₄ alkyl-C(=O)O-, C₃₋₆ cycloalkyl-oxy-, C₃₋₆ cycloalkylmethyl-oxy-;
C₁₋₆ alkyl substituted with OH, methoxy, ethoxy, propoxy, or butoxy; and
C₂₋₆ alkenyl substituted with OH, methoxy, ethoxy, propoxy, or butoxy;

R⁴¹, at each occurrence, is independently selected from

20 H, CF₃, halo, OH, CO₂H, SO₂R⁴⁵, NR⁴⁶R⁴⁷, NO₂, CN,
C₂₋₄ alkenyl, C₂₋₄ alkynyl, C₁₋₃ alkoxy, C₁₋₃ haloalkyl, and C₁₋₃ alkyl;

R⁴², at each occurrence, is independently selected from

25 H, CF₃, halo, OH, CO₂H, SO₂R⁴⁵, NR⁴⁶R⁴⁷, NO₂, CN, CH(=NH)NH₂,
NHC(=NH)NH₂,
C₂₋₄ alkenyl, C₂₋₄ alkynyl, C₁₋₃ alkoxy, C₁₋₃ haloalkyl, C₃₋₆ cycloalkyl, and
C₁₋₃ alkyl;

R⁴³ is cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, phenyl, or pyridyl, each substituted with 0-3 R⁴⁴;

5 R⁴⁴, at each occurrence, is independently selected from H, halo, -OH, NR⁴⁶R⁴⁷, CO₂H, SO₂R⁴⁵, -CF₃, -OCF₃, -CN, -NO₂, methyl, ethyl, propyl, butyl, methoxy, ethoxy, propoxy, and butoxy;

R⁴⁵ is methyl, ethyl, propyl, or butyl;

10 R⁴⁶, at each occurrence, is independently selected from H, methyl, ethyl, propyl, and butyl;

R⁴⁷, at each occurrence, is independently selected from from H, methyl, ethyl, propyl, and butyl;

15

k is 1;

m is 1; and

n is 0, 1 or 2.

20

In a more preferred embodiment, the present invention provides the method as defined in Claim 19 where in the compound administered:

X is -CH₂-;

25

R¹ is selected from H,

C₁₋₅ alkyl substituted with 0-1 R²,

C₂₋₅ alkenyl substituted with 0-1 R², and

C₂₋₃ alkynyl substituted with 0-1 R²;

30

R² is C₃₋₆ cycloalkyl;

R⁵ is H, methyl, ethyl, or propyl;

5 R^{6a} is H, methyl, or ethyl;

R^{6b} is H;

10 R⁷ and R⁹, at each occurrence, are independently selected from
H, F, Cl, -CH₃, -OCH₃, -CF₃, -OCF₃, -CN, and -NO₂,

R⁸ is selected from

15 methyl substituted with R¹¹;
ethenyl substituted with R¹¹;
OR¹², SR¹², NR¹²R¹³, NR¹²C(O)R¹⁵, NR¹²C(O)OR¹⁵, NR¹²S(O)₂R¹⁵,
and NR¹²C(O)NHR¹⁵;

R¹¹ is selected from

20 phenyl- substituted with 0-5 fluoro;
2-(H₃CCH₂C(=O))-phenyl- substituted with R³³;
2-(H₃CC(=O))-phenyl- substituted with R³³;
2-(HC(=O))-phenyl- substituted with R³³;
2-(H₃CCH(OH))-phenyl- substituted with R³³;
2-(H₃CCH₂CH(OH))-phenyl- substituted with R³³;
25 2-(HOCH₂)-phenyl- substituted with R³³;
2-(HOCH₂CH₂)-phenyl- substituted with R³³;
2-(H₃COCH₂)-phenyl- substituted with R³³;
2-(H₃COCH₂CH₂)-phenyl- substituted with R³³;

- 2-(H₃CCH(OMe))-phenyl- substituted with R³³;
 2-(H₃COC(=O))-phenyl- substituted with R³³;
 2-(HOCH₂CH=CH)-phenyl- substituted with R³³;
 2-((MeOC=O)CH=CH)-phenyl- substituted with R³³;
 5 2-(methyl)-phenyl- substituted with R³³;
 2-(ethyl)-phenyl- substituted with R³³;
 2-(i-propyl)-phenyl- substituted with R³³;
 2-(F₃C)-phenyl- substituted with R³³;
 2-(NC)-phenyl- substituted with R³³;
 10 2-(H₃CO)-phenyl- substituted with R³³;
 2-(fluoro)-phenyl- substituted with R³³;
 2-(chloro)-phenyl- substituted with R³³;
 3-(NC)-phenyl- substituted with R³³;
 3-(H₃CO)-phenyl- substituted with R³³;
 15 3-(fluoro)-phenyl- substituted with R³³;
 3-(chloro)-phenyl- substituted with R³³;
 4-(NC)-phenyl- substituted with R³³;
 4-(fluoro)-phenyl- substituted with R³³;
 4-(chloro)-phenyl- substituted with R³³;
 20 4-(H₃CS)-phenyl- substituted with R³³;
 4-(H₃CO)-phenyl- substituted with R³³;
 4-(ethoxy)-phenyl- substituted with R³³;
 4-(i-propoxy)-phenyl- substituted with R³³;
 4-(i-butoxy)-phenyl- substituted with R³³;
 25 4-(H₃CCH₂CH₂C(=O))-phenyl- substituted with R³³;
 4-((H₃C)₂CHC(=O))-phenyl- substituted with R³³;
 4-(H₃CCH₂C(=O))-phenyl- substituted with R³³;

- 4-(H₃CC(=O))-phenyl- substituted with R³³;
- 4-(H₃CCH₂CH₂CH(OH))-phenyl- substituted with R³³;
- 4-((H₃C)₂CHCH(OH))-phenyl- substituted with R³³;
- 4-(H₃CCH₂CH(OH))-phenyl- substituted with R³³;
- 5 4-(H₃CCH(OH))-phenyl- substituted with R³³;
- 4-(cyclopropyloxy)-phenyl- substituted with R³³;
- 4-(cyclobutyloxy)-phenyl- substituted with R³³; and
- 4-(cyclopentyloxy)-phenyl- substituted with R³³;
- 10 R¹² is selected from
- phenyl- substituted with 0-5 fluoro;
- 2-(H₃CCH₂C(=O))-phenyl- substituted with R³³;
- 2-(H₃CC(=O))-phenyl- substituted with R³³;
- 2-(HC(=O))-phenyl- substituted with R³³;
- 15 2-(H₃CCH(OH))-phenyl- substituted with R³³;
- 2-(H₃CCH₂CH(OH))-phenyl- substituted with R³³;
- 2-(HOCH₂)-phenyl- substituted with R³³;
- 2-(HOCH₂CH₂)-phenyl- substituted with R³³;
- 2-(H₃COCH₂)-phenyl- substituted with R³³;
- 20 2-(H₃COCH₂CH₂)-phenyl- substituted with R³³;
- 2-(H₃CCH(OMe))-phenyl- substituted with R³³;
- 2-(H₃COC(=O))-phenyl- substituted with R³³;
- 2-(HOCH₂CH=CH)-phenyl- substituted with R³³;
- 2-((MeOC=O)CH=CH)-phenyl- substituted with R³³;
- 25 2-(methyl)-phenyl- substituted with R³³;
- 2-(ethyl)-phenyl- substituted with R³³;
- 2-(i-propyl)-phenyl- substituted with R³³;

- 2-(F₃C)-phenyl- substituted with R³³;
 2-(NC)-phenyl- substituted with R³³;
 2-(H₃CO)-phenyl- substituted with R³³;
 2-(fluoro)-phenyl- substituted with R³³;
 5 2-(chloro)-phenyl- substituted with R³³;
 3-(NC)-phenyl- substituted with R³³;
 3-(H₃CO)-phenyl- substituted with R³³;
 3-(fluoro)-phenyl- substituted with R³³;
 3-(chloro)-phenyl- substituted with R³³;
 10 4-(NC)-phenyl- substituted with R³³;
 4-(fluoro)-phenyl- substituted with R³³;
 4-(chloro)-phenyl- substituted with R³³;
 4-(H₃CS)-phenyl- substituted with R³³;
 4-(H₃CO)-phenyl- substituted with R³³;
 15 4-(ethoxy)-phenyl- substituted with R³³;
 4-(i-propoxy)-phenyl- substituted with R³³;
 4-(i-butoxy)-phenyl- substituted with R³³;
 4-(H₃CCH₂CH₂C(=O))-phenyl- substituted with R³³;
 4-((H₃C)₂CHC(=O))-phenyl- substituted with R³³;
 20 4-(H₃CCH₂C(=O))-phenyl- substituted with R³³;
 4-(H₃CC(=O))-phenyl- substituted with R³³;
 4-(H₃CCH₂CH₂CH(OH))-phenyl- substituted with R³³;
 4-((H₃C)₂CHCH(OH))-phenyl- substituted with R³³;
 4-(H₃CCH₂CH(OH))-phenyl- substituted with R³³;
 25 4-(H₃CCH(OH))-phenyl- substituted with R³³;
 4-(cyclopropyloxy)-phenyl- substituted with R³³;
 4-(cyclobutyloxy)-phenyl- substituted with R³³; and

4-(cyclopentyloxy)-phenyl- substituted with R³³;

R¹³ is H, methyl, or ethyl;

5 alternatively, R¹² and R¹³ join to form a 5- or 6-membered ring selected from
pyrrolyl, pyrrolidinyl, imidazolyl, piperidinyl, piperizinyll,
methylpiperizinyll, and morpholinyl;

alternatively, R¹² and R¹³ when attached to N may be combined to form a 9- or 10-
10 membered bicyclic heterocyclic ring system containing from 1-3 heteroatoms
selected from the group consisting of N, O, and S; wherein said bicyclic
heterocyclic ring system is selected from indolyl, indolinyl, indazolyl,
benzimidazolyl, benzimidazolinyl, benztriazolyl, benzoxazolyl,
benzoxazolinyl, benzthiazolyl, and dioxobenzthiazolyl; wherein said bicyclic
15 heterocyclic ring system is substituted with 0-1 R¹⁶;

R¹⁵ is H, methyl, ethyl, propyl, or butyl;

R¹⁶, at each occurrence, is independently selected from
20 H, OH, F, Cl, CN, NO₂, methyl, ethyl, methoxy, ethoxy, trifluoromethyl, and
trifluoromethoxy;

R³³, at each occurrence, is independently selected from
H, F, Cl, -CH₃, -OCH₃, -CF₃, -OCF₃, -CN, and -NO₂;

25

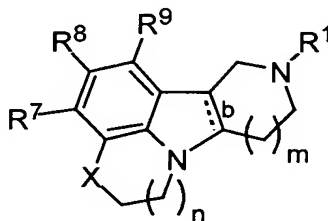
k is 1;

m is 1; and

n is 1 or 2.

30

In a more preferred embodiment, the present invention provides the method as defined in Claim 19 where the compound administered is a compound of Formula (I-a):



(I-a)

wherein:

b is a single bond;

X is -CH₂-, -CH(OH)-, or -C(=O)-;

R¹ is selected from

- hydrogen, methyl, ethyl, n-propyl, n-butyl, s-butyl,
- t-butyl, n-pentyl, n-hexyl, 2-propyl, 2-butyl, 2-pentyl, 2-hexyl, 2-methylpropyl,
- 2-methylbutyl, 2-methylpentyl, 2-ethylbutyl, 3-methylpentyl, 3-
- methylbutyl,
- 4-methylpentyl, 2-fluoroethyl, 2,2-difluoroethyl,
- 2,2,2-trifluoroethyl,
- 2-propenyl, 2-methyl-2-propenyl, trans-2-butenyl,
- 3-methyl-butenyl, 3-butenyl, trans-2-pentenyl,
- cis-2-pentenyl, 4-pentenyl, 4-methyl-3-pentenyl,
- 3,3-dichloro-2-propenyl, trans-3-phenyl-2-propenyl,

- cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cyclopropylmethyl,
cyclobutylmethyl, cyclopentylmethyl, cyclohexylmethyl,
- benzyl, 2-methylbenzyl, 3-methylbenzyl, 4-methylbenzyl, 2,5-dimethylbenzyl,
2,4-dimethylbenzyl, 3,5-dimethylbenzyl,
2,4,6-trimethyl-benzyl, 3-methoxy-benzyl, 3,5-dimethoxy-benzyl,
pentafluorobenzyl, 2-phenylethyl, 1-phenyl-2-propyl, 4-phenylbutyl, 4-phenylbenzyl, 2-phenylbenzyl,
- (2,3-dimethoxy-phenyl)C(=O)-, (2,5-dimethoxy-phenyl)C(=O)-, (3,4-dimethoxy-phenyl)C(=O)-,
(3,5-dimethoxy-phenyl)C(=O)-, cyclopropyl-C(=O)-,
isopropyl-C(=O)-, ethyl-CO₂-, propyl-CO₂-, t-butyl-CO₂-,
2,6-dimethoxy-benzyl, 2,4-dimethoxy-benzyl,
2,4,6-trimethoxy-benzyl, 2,3-dimethoxy-benzyl,
2,4,5-trimethoxy-benzyl, 2,3,4-trimethoxy-benzyl,
3,4-dimethoxy-benzyl, 3,4,5-trimethoxy-benzyl,
(4-fluoro-phenyl)ethyl,
- CH=CH₂, -CH₂-CH=CH₂, -CH=CH-CH₃, -C≡CH, -C≡C-CH₃, and
-CH₂-C≡CH;
- R⁷, R⁸, and R⁹, at each occurrence, are independently selected from
hydrogen, fluoro, chloro, bromo, cyano, methyl, ethyl, propyl, isopropyl, butyl,
t-butyl, nitro, trifluoromethyl, methoxy, ethoxy, isopropoxy,
trifluoromethoxy, phenyl,
- methylC(=O)-, ethylC(=O)-, propylC(=O)-, isopropylC(=O)-, butylC(=O)-,
phenylC(=O)-,

- methylCO₂-, ethylCO₂-, propylCO₂-, isopropylCO₂-, butylCO₂-,
phenylCO₂-,
- 5 dimethylamino-S(=O)-, diethylamino-S(=O)-,
dipropylamino-S(=O)-, di-isopropylamino-S(=O)-, dibutylamino-S(=O)-,
diphenylamino-S(=O)-,
- 10 dimethylamino-SO₂-, diethylamino-SO₂-, dipropylamino-SO₂-, di-
isopropylamino-SO₂-, dibutylamino-SO₂-,
diphenylamino-SO₂-,
- 15 dimethylamino-C(=O)-, diethylamino-C(=O)-,
dipropylamino-C(=O)-, di-isopropylamino-C(=O)-, dibutylamino-C(=O)-,
diphenylamino-C(=O)-,
- 20 2-chlorophenyl, 2-fluorophenyl, 2-bromophenyl, 2-cyanophenyl, 2-
methylphenyl, 2-trifluoromethylphenyl,
2-methoxyphenyl, 2-trifluoromethoxyphenyl,
- 25 3-chlorophenyl, 3-fluorophenyl, 3-bromophenyl,
3-cyanophenyl, 3-methylphenyl, 3-ethylphenyl,
3-propylphenyl, 3-isopropylphenyl, 3-butylphenyl,
3-trifluoromethylphenyl, 3-methoxyphenyl,
3-isopropoxyphenyl, 3-trifluoromethoxyphenyl,
- 30 4-chlorophenyl, 4-fluorophenyl, 4-bromophenyl,
4-cyanophenyl, 4-methylphenyl, 4-ethylphenyl,
4-propylphenyl, 4-isopropylphenyl, 4-butylphenyl,
4-trifluoromethylphenyl, 4-methoxyphenyl,
4-isopropoxyphenyl, 4-trifluoromethoxyphenyl,

- 4-thiomethoxyphenyl,
- 2,3-dichlorophenyl, 2,3-difluorophenyl, 2,3-dimethylphenyl,
2,3-ditrifluoromethylphenyl, 2,3-dimethoxyphenyl,
5 2,3-ditrifluoromethoxyphenyl,
- 2,4-dichlorophenyl, 2,4-difluorophenyl, 2,4-dimethylphenyl,
2,4-ditrifluoromethylphenyl, 2,4-dimethoxyphenyl,
2,4-ditrifluoromethoxyphenyl,
10
- 2,5-dichlorophenyl, 2,5-difluorophenyl, 2,5-dimethylphenyl,
2,5-ditrifluoromethylphenyl, 2,5-dimethoxyphenyl,
2,5-ditrifluoromethoxyphenyl,
- 15 2,6-dichlorophenyl, 2,6-difluorophenyl, 2,6-dimethylphenyl,
2,6-ditrifluoromethylphenyl, 2,6-dimethoxyphenyl,
2,6-ditrifluoromethoxyphenyl,
- 3,4-dichlorophenyl, 3,4-difluorophenyl, 3,4-dimethylphenyl,
20 3,4-ditrifluoromethylphenyl, 3,4-dimethoxyphenyl,
3,4-ditrifluoromethoxyphenyl,
- 2,4,6-trichlorophenyl, 2,4,6-trifluorophenyl,
2,4,6-trimethylphenyl, 2,4,6-tritrifluoromethylphenyl,
25 2,4,6-trimethoxyphenyl, 2,4,6-tritrifluoromethoxyphenyl,
- 2-chloro-4-CF₃-phenyl, 2-fluoro-3-chloro-phenyl,
2-chloro-4-CF₃-phenyl, 2-chloro-4-methoxy-phenyl,
2-methoxy-4-isopropyl-phenyl, 2-CF₃-4-methoxy-phenyl,
30 2-methyl-4-methoxy-5-fluoro-phenyl,
2-methyl-4-methoxy-phenyl, 2-chloro-4-CF₃O-phenyl,

- 2,4,5-trimethyl-phenyl, 2-methyl-4-chloro-phenyl,
- methyl-C(=O)NH-, ethyl-C(=O)NH-, propyl-C(=O)NH-,
isopropyl-C(=O)NH-, butyl-C(=O)NH-, phenyl-C(=O)NH-,
- 5 4-acetylphenyl, 3-acetamidophenyl, 4-pyridyl, 2-furanyl,
2-thiophenyl, 2-naphthyl;
- 10 2-Me-5-F-phenyl, 2-F-5-Me-phenyl, 2-MeO-5-F-phenyl,
2-Me-3-Cl-phenyl, 3-NO₂-phenyl, 2-NO₂-phenyl,
2-Cl-3-Me-phenyl, 2-Me-4-EtO-phenyl, 2-Me-4-F-phenyl,
2-Cl-6-F-phenyl, 2-Cl-4-(CHF₂)O-phenyl,
2,4-diMeO-6-F-phenyl, 2-CF₃-6-F-phenyl,
2-MeS-phenyl, 2,6-diCl-4-MeO-phenyl,
- 15 2,3,4-triF-phenyl, 2,6-diF-4-Cl-phenyl,
2,3,4,6-tetraF-phenyl, 2,3,4,5,6-pentaF-phenyl,
2-CF₃-4-EtO-phenyl, 2-CF₃-4-iPrO-phenyl,
2-CF₃-4-Cl-phenyl, 2-CF₃-4-F-phenyl, 2-Cl-4-EtO-phenyl,
2-Cl-4-iPrO-phenyl, 2-Et-4-MeO-phenyl,
- 20 2-CHO-4-MeO-phenyl, 2-CH(OH)Me-4-MeO-phenyl,
2-CH(OMe)Me-4-MeO-phenyl, 2-C(=O)Me-4-MeO-phenyl,
2-CH₂(OH)-4-MeO-phenyl, 2-CH₂(OMe)-4-MeO-phenyl,
2-CH(OH)Et-4-MeO-phenyl, 2-C(=O)Et-4-MeO-phenyl,
(Z)-2-CH=CHCO₂Me-4-MeO-phenyl,
- 25 2-CH₂CH₂CO₂Me-4-MeO-phenyl,
(Z)-2-CH=CHCH₂(OH)-4-MeO-phenyl,
(E)-2-CH=CHCO₂Me-4-MeO-phenyl,
(E)-2-CH=CHCH₂(OH)-4-MeO-phenyl,
2-CH₂CH₂OMe-4-MeO-phenyl,
- 30 2-F-4-MeO-phenyl, 2-Cl-4-F-phenyl,

(2-Cl-phenyl)-CH=CH-, (3-Cl-phenyl)-CH=CH-,
 (2,6-diF-phenyl)-CH=CH-, -CH₂CH=CH₂,
 phenyl-CH=CH-, (2-Me-4-MeO-phenyl)-CH=CH-,
 cyclohexyl, cyclopentyl, cyclohexylmethyl,
 5 -CH₂CH₂CO₂Et, -(CH₂)₃CO₂Et, -(CH₂)₄CO₂Et,
 benzyl, 2-F-benzyl, 3-F-benzyl, 4-F-benzyl,
 3-MeO-benzyl, 3-OH-benzyl, 2-MeO-benzyl,
 2-OH-benzyl, 2-CO₂Me-3-MeO-phenyl,
 2-Me-4-CN-phenyl, 2-Me-3-CN-phenyl, 2-CF₃-4-CN-phenyl,
 10 3-CHO-phenyl, 3-CH₂(OH)-phenyl, 3-CH₂(OMe)-phenyl,
 3-CH₂(NMe₂)-phenyl, 3-CN-4-F-phenyl,
 3-CONH₂-4-F-phenyl, 2-CH₂(NH₂)-4-MeO-phenyl-,
 phenyl-NH-, (4-F-phenyl)-NH-, (2,4-diCl-phenyl)-NH-,
 phenyl-C(=O)NH-, benzyl-NH-, (2-Me-4-MeO-phenyl)-NH-,
 15 (2-F-4-MeO-phenyl)-NH-, (2-Me-4-F-phenyl)-NH-,
 phenyl-S-, -NMe₂, 1-pyrrolidinyl, and
 -N(tosylate)₂,

provided that two of R⁷, R⁸, and R⁹, are independently selected from hydrogen,
 20 fluoro, chloro, bromo, cyano, methyl, ethyl, propyl, isopropyl, butyl, t-butyl,
 nitro, trifluoromethyl, methoxy, ethoxy, isopropoxy, and trifluoromethoxy;

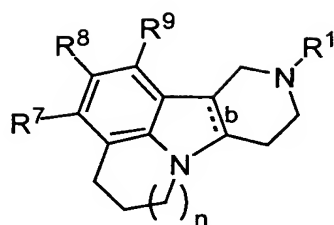
m is 1; and

n is 0, 1 or 2.

25

In a more preferred embodiment, the present invention provides the method as
 defined in Claim 24 where the compound administered is a compound of Formula
 (V):

30



(V)

wherein:

5

b is a single bond, wherein the bridge hydrogens are in a cis position;

R¹ is selected from

- hydrogen, methyl, ethyl, n-propyl, n-butyl, s-butyl,
 10 t-butyl, n-pentyl, n-hexyl, 2-propyl, 2-butyl, 2-pentyl, 2-hexyl, 2-methylpropyl,
 2-methylbutyl, 2-methylpentyl, 2-ethylbutyl, 3-methylpentyl, 3-
 methylbutyl,
 4-methylpentyl, 2-fluoroethyl, 2,2-difluoroethyl,
 2,2,2-trifluoroethyl, 2-propenyl, 2-methyl-2-propenyl, trans-2-butenyl, 3-
 15 methyl-butenyl, 3-butenyl,
 trans-2-pentenyl, cis-2-pentenyl, 4-pentenyl,
 4-methyl-3-pentenyl, 3,3-dichloro-2-propenyl,
 trans-3-phenyl-2-propenyl, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl,
 cyclopropylmethyl, cyclobutylmethyl, cyclopentylmethyl,
 20 cyclohexylmethyl,
 -CH=CH₂, -CH₂-CH=CH₂, -CH=CH-CH₃, -C≡CH, -C≡C-CH₃,
 and -CH₂-C≡CH;

R⁷ and R⁹, at each occurrence, are independently selected from hydrogen, fluoro,
 25 methyl, trifluoromethyl, and methoxy;

R⁸ is selected from

- hydrogen, fluoro, chloro, bromo, cyano, methyl, ethyl, propyl, isopropyl, butyl,
t-butyl, nitro, trifluoromethyl, methoxy, ethoxy, isopropoxy,
trifluoromethoxy, phenyl,
- 5 methylC(=O)-, ethylC(=O)-, propylC(=O)-, isopropylC(=O)-, butylC(=O)-,
phenylC(=O)-,
- methylCO₂-, ethylCO₂-, propylCO₂-, isopropylCO₂-, butylCO₂-,
phenylCO₂-,
- 10 dimethylamino-S(=O)-, diethylamino-S(=O)-,
dipropylamino-S(=O)-, di-isopropylamino-S(=O)-, dibutylamino-S(=O)-,
diphenylamino-S(=O)-,
- 15 dimethylamino-SO₂-, diethylamino-SO₂-, dipropylamino-SO₂-, di-
isopropylamino-SO₂-, dibutylamino-SO₂-,
diphenylamino-SO₂-,
- 20 dimethylamino-C(=O)-, diethylamino-C(=O)-,
dipropylamino-C(=O)-, di-isopropylamino-C(=O)-, dibutylamino-C(=O)-,
diphenylamino-C(=O)-,
- 2-chlorophenyl, 2-fluorophenyl, 2-bromophenyl, 2-cyanophenyl, 2-
methylphenyl, 2-trifluoromethylphenyl,
- 25 2-methoxyphenyl, 2-trifluoromethoxyphenyl,
- 3-chlorophenyl, 3-fluorophenyl, 3-bromophenyl,
3-cyanophenyl, 3-methylphenyl, 3-ethylphenyl,
3-propylphenyl, 3-isopropylphenyl, 3-butylphenyl,
- 30 3-trifluoromethylphenyl, 3-methoxyphenyl,
3-isopropoxyphenyl, 3-trifluoromethoxyphenyl,

- 3-thiomethoxyphenyl,
- 4-chlorophenyl, 4-fluorophenyl, 4-bromophenyl,
 4-cyanophenyl, 4-methylphenyl, 4-ethylphenyl,
 5 4-propylphenyl, 4-isopropylphenyl, 4-butylphenyl,
 4-trifluoromethylphenyl, 4-methoxyphenyl,
 4-isopropoxyphenyl, 4-trifluoromethoxyphenyl,
 4-thiomethoxyphenyl,
- 10 2,3-dichlorophenyl, 2,3-difluorophenyl, 2,3-dimethylphenyl,
 2,3-ditrifluoromethylphenyl, 2,3-dimethoxyphenyl,
 2,3-ditrifluoromethoxyphenyl,
- 15 2,4-dichlorophenyl, 2,4-difluorophenyl, 2,4-dimethylphenyl,
 2,4-ditrifluoromethylphenyl, 2,4-dimethoxyphenyl,
 2,4-ditrifluoromethoxyphenyl,
- 20 2,5-dichlorophenyl, 2,5-difluorophenyl, 2,5-dimethylphenyl,
 2,5-ditrifluoromethylphenyl, 2,5-dimethoxyphenyl,
 2,5-ditrifluoromethoxyphenyl,
- 25 2,6-dichlorophenyl, 2,6-difluorophenyl, 2,6-dimethylphenyl,
 2,6-ditrifluoromethylphenyl, 2,6-dimethoxyphenyl,
 2,6-ditrifluoromethoxyphenyl,
- 30 3,4-dichlorophenyl, 3,4-difluorophenyl, 3,4-dimethylphenyl,
 3,4-ditrifluoromethylphenyl, 3,4-dimethoxyphenyl,
 3,4-ditrifluoromethoxyphenyl,
- 2,4,6-trichlorophenyl, 2,4,6-trifluorophenyl,
 2,4,6-trimethylphenyl, 2,4,6-tritrifluoromethylphenyl,
 2,4,6-trimethoxyphenyl, 2,4,6-tritrifluoromethoxyphenyl,

- 2-chloro-4-CF₃-phenyl, 2-fluoro-3-chloro-phenyl,
 2-chloro-4-CF₃-phenyl, 2-chloro-4-methoxy-phenyl,
 2-methoxy-4-isopropyl-phenyl, 2-CF₃-4-methoxy-phenyl,
 5 2-methyl-4-methoxy-5-fluoro-phenyl,
 2-methyl-4-methoxy-phenyl, 2-chloro-4-CF₃O-phenyl,
 2,4,5-trimethyl-phenyl, 2-methyl-4-chloro-phenyl,
- 10 methyl-C(=O)NH-, ethyl-C(=O)NH-, propyl-C(=O)NH-,
 isopropyl-C(=O)NH-, butyl-C(=O)NH-, phenyl-C(=O)NH-,
- 4-acetylphenyl, 3-acetamidophenyl, 4-pyridyl, 2-furanyl,
 2-thiophenyl, 2-naphthyl;
- 15 2-Me-5-F-phenyl, 2-F-5-Me-phenyl, 2-MeO-5-F-phenyl,
 2-Me-3-Cl-phenyl, 3-NO₂-phenyl, 2-NO₂-phenyl,
 2-Cl-3-Me-phenyl, 2-Me-4-EtO-phenyl, 2-Me-4-F-phenyl,
 2-Cl-6-F-phenyl, 2-Cl-4-(CHF₂)O-phenyl,
 2,4-diMeO-6-F-phenyl, 2-CF₃-6-F-phenyl,
 20 2-MeS-phenyl, 2,6-diCl-4-MeO-phenyl,
 2,3,4-triF-phenyl, 2,6-diF-4-Cl-phenyl,
 2,3,4,6-tetraF-phenyl, 2,3,4,5,6-pentaF-phenyl,
 2-CF₃-4-EtO-phenyl, 2-CF₃-4-iPrO-phenyl,
 2-CF₃-4-Cl-phenyl, 2-CF₃-4-F-phenyl, 2-Cl-4-EtO-phenyl,
 25 2-Cl-4-iPrO-phenyl, 2-Et-4-MeO-phenyl,
 2-CHO-4-MeO-phenyl, 2-CH(OH)Me-4-MeO-phenyl,
 2-CH(OMe)Me-4-MeO-phenyl, 2-C(=O)Me-4-MeO-phenyl,
 2-CH₂(OH)-4-MeO-phenyl, 2-CH₂(OMe)-4-MeO-phenyl,
 2-CH(OH)Et-4-MeO-phenyl, 2-C(=O)Et-4-MeO-phenyl,
 30 (Z)-2-CH=CHCO₂Me-4-MeO-phenyl,

- 2-CH₂CH₂CO₂Me-4-MeO-phenyl,
 (Z)-2-CH=CHCH₂(OH)-4-MeO-phenyl,
 (E)-2-CH=CHCO₂Me-4-MeO-phenyl,
 (E)-2-CH=CHCH₂(OH)-4-MeO-phenyl,
 5 2-CH₂CH₂OMe-4-MeO-phenyl,
 2-F-4-MeO-phenyl, 2-Cl-4-F-phenyl,
 (2-Cl-phenyl)-CH=CH-, (3-Cl-phenyl)-CH=CH-,
 (2,6-diF-phenyl)-CH=CH-, -CH₂CH=CH₂,
 phenyl-CH=CH-, (2-Me-4-MeO-phenyl)-CH=CH-,
 10 cyclohexyl, cyclopentyl, cyclohexylmethyl,
 -CH₂CH₂CO₂Et, -(CH₂)₃CO₂Et, -(CH₂)₄CO₂Et,
 benzyl, 2-F-benzyl, 3-F-benzyl, 4-F-benzyl,
 3-MeO-benzyl, 3-OH-benzyl, 2-MeO-benzyl,
 2-OH-benzyl, 2-CO₂Me-3-MeO-phenyl,
 15 2-Me-4-CN-phenyl, 2-Me-3-CN-phenyl, 2-CF₃-4-CN-phenyl,
 3-CHO-phenyl, 3-CH₂(OH)-phenyl, 3-CH₂(OMe)-phenyl,
 3-CH₂(NMe₂)-phenyl, 3-CN-4-F-phenyl,
 3-CONH₂-4-F-phenyl, 2-CH₂(NH₂)-4-MeO-phenyl-,
 phenyl-NH-, (4-F-phenyl)-NH-, (2,4-diCl-phenyl)-NH-,
 20 phenyl-C(=O)NH-, benzyl-NH-, (2-Me-4-MeO-phenyl)-NH-,
 (2-F-4-MeO-phenyl)-NH-, (2-Me-4-F-phenyl)-NH-,
 phenyl-S-, -NMe₂, 1-pyrrolidinyl, and
 -N(tosylate)₂; and
 25 n is 0, 1 or 2.

In a more preferred embodiment, the present invention provides the method as defined in Claim 18 where in the compound administered:

30

X is $-\text{CHR}^{10}-$ or $-\text{C}(=\text{O})-$;

R^1 is selected from

- C₁₋₆ alkyl substituted with Z,
- 5 C₂₋₆ alkenyl substituted with Z,
- C₂₋₆ alkynyl substituted with Z,
- C₃₋₆ cycloalkyl substituted with Z,
- aryl substituted with Z,
- 5-6 membered heterocyclic ring system containing at least one heteroatom
- 10 selected from the group consisting of N, O, and S, said heterocyclic ring system substituted with Z;
- C₁₋₆ alkyl substituted with 0-2 R^2 ,
- C₂₋₆ alkenyl substituted with 0-2 R^2 ,
- C₂₋₆ alkynyl substituted with 0-2 R^2 ,
- 15 aryl substituted with 0-2 R^2 , and
- 5-6 membered heterocyclic ring system containing at least one heteroatom
- selected from the group consisting of N, O, and S, said heterocyclic ring system substituted with 0-2 R^2 ;

20 Z is selected from H,

- $-\text{CH}(\text{OH})\text{R}^2$,
- $-\text{C}(\text{ethylenedioxy})\text{R}^2$,
- $-\text{OR}^2$,
- $-\text{SR}^2$,
- 25 $-\text{NR}^2\text{R}^3$,
- $-\text{C}(\text{O})\text{R}^2$,
- $-\text{C}(\text{O})\text{NR}^2\text{R}^3$,
- $-\text{NR}^3\text{C}(\text{O})\text{R}^2$,
- $-\text{C}(\text{O})\text{OR}^2$,

-OC(O)R²,
 -CH(=NR⁴)NR²R³,
 -NHC(=NR⁴)NR²R³,
 -S(O)R²,
 5 -S(O)₂R²,
 -S(O)₂NR²R³, and -NR³S(O)₂R²;

R², at each occurrence, is independently selected from
 C₁₋₄ alkyl,
 10 C₂₋₄ alkenyl,
 C₂₋₄ alkynyl,
 C₃₋₆ cycloalkyl,
 aryl substituted with 0-5 R⁴²,
 C₃₋₁₀ carbocyclic group substituted with 0-3 R⁴¹, and
 15 5-10 membered heterocyclic ring system containing from 1-4 heteroatoms
 selected from the group consisting of N, O, and S substituted with 0-3
 R⁴¹;

R³, at each occurrence, is independently selected from
 20 H, C₁₋₄ alkyl, C₂₋₄ alkenyl, C₂₋₄ alkynyl, and
 C₁₋₄ alkoxy;

alternatively, R² and R³ join to form a 5- or 6-membered ring optionally substituted
 with -O- or -N(R⁴)-;

25

R⁴, at each occurrence, is independently selected from H, methyl, ethyl, propyl, and
 butyl;

R⁵ is H, methyl, ethyl, propyl, or butyl;

R^{6a} is selected from

H, -OH, -NR⁴⁶R⁴⁷, -CF₃,

C₁₋₄ alkyl, C₂₋₄ alkenyl, C₂₋₄ alkynyl, C₁₋₄ alkoxy, C₁₋₄ haloalkyl, C₃₋₆

5 cycloalkyl, and

aryl substituted with 0-3 R⁴⁴;

R^{6b} is H;

10 R⁷, R⁸, and R⁹, at each occurrence, are independently selected from

H, halo, -CF₃, -OCF₃, -OH, -CN, -NO₂, -NR⁴⁶R⁴⁷,

C₁₋₈ alkyl, C₂₋₈ alkenyl, C₂₋₈ alkynyl, C₁₋₄ haloalkyl, C₁₋₈ alkoxy, (C₁₋₄
haloalkyl)oxy,

C₁₋₄ alkyl substituted with 0-2 R¹¹,

15 C₃₋₁₀ carbocyclic group substituted with 0-3 R³³,

aryl substituted with 0-5 R³³,

5-10 membered heterocyclic ring system containing from 1-4 heteroatoms

selected from the group consisting of N, O, and S substituted with 0-3

R³¹;

20

OR¹², SR¹², NR¹²R¹³, C(O)H, C(O)R¹², C(O)NR¹²R¹³, NR¹⁴C(O)R¹²,

C(O)OR¹², OC(O)R¹², OC(O)OR¹², CH(=NR¹⁴)NR¹²R¹³,

NHC(=NR¹⁴)NR¹²R¹³, S(O)R¹², S(O)₂R¹², S(O)NR¹²R¹³,

S(O)₂NR¹²R¹³, NR¹⁴S(O)R¹², NR¹⁴S(O)₂R¹², NR¹²C(O)R¹⁵,

25 NR¹²C(O)OR¹⁵, NR¹²S(O)₂R¹⁵, and NR¹²C(O)NHR¹⁵;

R¹⁰ is selected from H, -OH,

C₁₋₆ alkyl substituted with 0-1 R^{10B},

C₂₋₆ alkenyl substituted with 0-1 R^{10B},
 C₂₋₆ alkynyl substituted with 0-1 R^{10B}, and
 C₁₋₆ alkoxy;

5 R^{10B} is selected from

C₁₋₄ alkoxy,
 C₃₋₆ cycloalkyl,
 C₃₋₁₀ carbocyclic group substituted with 0-3 R³³,
 phenyl substituted with 0-3 R³³, and

10 5-6 membered heterocyclic ring system containing 1, 2, or 3 heteroatoms
 selected from the group consisting of N, O, and S substituted with 0-2
 R⁴⁴;

R¹¹ is selected from

15 H, halo, -CF₃, -CN, -NO₂,
 C₁₋₈ alkyl, C₂₋₈ alkenyl, C₂₋₈ alkynyl, C₁₋₄ haloalkyl, C₁₋₈ alkoxy, C₃₋₁₀
 cycloalkyl,

C₃₋₁₀ carbocyclic group substituted with 0-3 R³³,
 aryl substituted with 0-5 R³³,

20 5-10 membered heterocyclic ring system containing from 1-4 heteroatoms
 selected from the group consisting of N, O, and S substituted with 0-3
 R³¹;

25 OR¹², SR¹², NR¹²R¹³, C(O)H, C(O)R¹², C(O)NR¹²R¹³, NR¹⁴C(O)R¹²,
 C(O)OR¹², OC(O)R¹², OC(O)OR¹², CH(=NR¹⁴)NR¹²R¹³,
 NHC(=NR¹⁴)NR¹²R¹³, S(O)R¹², S(O)₂R¹², S(O)NR¹²R¹³,
 S(O)₂NR¹²R¹³, NR¹⁴S(O)R¹², and NR¹⁴S(O)₂R¹²;

R¹², at each occurrence, is independently selected from

- C₁₋₄ alkyl,
- C₂₋₄ alkenyl,
- C₂₋₄ alkynyl,
- 5 C₃₋₆ cycloalkyl,
- phenyl substituted with 0-5 R³³;
- C₃₋₁₀ carbocyclic group substituted with 0-3 R³³, and
- 5-10 membered heterocyclic ring system containing from 1-4 heteroatoms
- selected from the group consisting of N, O, and S substituted with 0-3
- 10 R³¹;

R¹³, at each occurrence, is independently selected from

H, C₁₋₄ alkyl, C₂₋₄ alkenyl, and C₂₋₄ alkynyl;

- 15 alternatively, R¹² and R¹³ join to form a 5- or 6-membered ring optionally substituted with -O- or -N(R¹⁴)-;

R¹⁴, at each occurrence, is independently selected from H and C₁₋₄ alkyl;

- 20 R³¹, at each occurrence, is independently selected from

H, OH, halo, CF₃, SO₂R⁴⁵, NR⁴⁶R⁴⁷, methyl, ethyl, and propyl;

R³³, at each occurrence, is independently selected from

- H, OH, halo, CN, NO₂, CF₃, SO₂R⁴⁵, NR⁴⁶R⁴⁷,
- 25 C₁₋₃ alkyl, C₂₋₃ alkenyl, C₂₋₃ alkynyl, C₃₋₅ cycloalkyl, C₁₋₃ haloalkyl, C₁₋₃
- haloalkyl-oxy-, C₁₋₃ alkyloxy-, C₁₋₃ alkylthio-, C₁₋₃ alkyl-C(=O)-,
- and C₁₋₃ alkyl-C(=O)NH-;

R⁴¹, at each occurrence, is independently selected from

H, CF₃, halo, OH, CO₂H, SO₂R⁴⁵, NR⁴⁶R⁴⁷, NO₂, CN, =O,

C₂₋₈ alkenyl, C₂₋₈ alkynyl, C₁₋₄ alkoxy, C₁₋₄ haloalkyl

C₁₋₄ alkyl substituted with 0-1 R⁴³,

aryl substituted with 0-3 R⁴², and

- 5 5-10 membered heterocyclic ring system containing from 1-4 heteroatoms
 selected from the group consisting of N, O, and S substituted with 0-3
 R⁴⁴;

R⁴², at each occurrence, is independently selected from

- 10 H, CF₃, halo, OH, CO₂H, SO₂R⁴⁵, SR⁴⁵, NR⁴⁶R⁴⁷, OR⁴⁸, NO₂, CN,
 CH(=NH)NH₂, NHC(=NH)NH₂,
 C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₁₋₄ alkoxy, C₁₋₄ haloalkyl, C₃₋₆ cycloalkyl,
 C₁₋₄ alkyl substituted with 0-1 R⁴³,
 aryl substituted with 0-3 R⁴⁴, and

- 15 5-10 membered heterocyclic ring system containing from 1-4 heteroatoms
 selected from the group consisting of N, O, and S substituted with 0-3
 R⁴⁴;

R⁴³ is C₃₋₆ cycloalkyl or aryl substituted with 0-3 R⁴⁴;

20

R⁴⁴, at each occurrence, is independently selected from H, halo, -OH, NR⁴⁶R⁴⁷,
CO₂H, SO₂R⁴⁵, -CF₃, -OCF₃, -CN, -NO₂, C₁₋₄ alkyl, and C₁₋₄ alkoxy;

R⁴⁵ is C₁₋₄ alkyl;

25

R⁴⁶, at each occurrence, is independently selected from H and C₁₋₄ alkyl;

R⁴⁷, at each occurrence, is independently selected from H, C₁₋₄ alkyl,
-C(=O)NH(C₁₋₄ alkyl), -SO₂(C₁₋₄ alkyl),
-SO₂(phenyl), -C(=O)O(C₁₋₄ alkyl), -C(=O)(C₁₋₄ alkyl), and -C(=O)H;

5 R⁴⁸, at each occurrence, is independently selected from H, C₁₋₄ alkyl,
-C(=O)NH(C₁₋₄ alkyl), -C(=O)O(C₁₋₄ alkyl),
-C(=O)(C₁₋₄ alkyl), and -C(=O)H;

k is 1 or 2;

10 m is 0, 1, or 2; and
n is 0, 1 or 2.

In a more preferred embodiment, the present invention provides the method as
15 defined in Claim 26 where in the compound administered:

X is -CHR¹⁰- or -C(=O)-;

R¹ is selected from

20 C₂₋₅ alkyl substituted with Z,
C₂₋₅ alkenyl substituted with Z,
C₂₋₅ alkynyl substituted with Z,
C₃₋₆ cycloalkyl substituted with Z,
aryl substituted with Z,
25 5-6 membered heterocyclic ring system containing at least one heteroatom
selected from the group consisting of N, O, and S, said heterocyclic
ring system substituted with Z;
C₁₋₅ alkyl substituted with 0-2 R²,
C₂₋₅ alkenyl substituted with 0-2 R², and

C₂₋₅ alkynyl substituted with 0-2 R²;

Z is selected from H,

- CH(OH)R²,
- 5 -C(ethylenedioxy)R²,
- OR²,
- SR²,
- NR²R³,
- C(O)R²,
- 10 -C(O)NR²R³,
- NR³C(O)R²,
- C(O)OR²,
- OC(O)R²,
- CH(=NR⁴)NR²R³,
- 15 -NHC(=NR⁴)NR²R³,
- S(O)R²,
- S(O)₂R²,
- S(O)₂NR²R³, and -NR³S(O)₂R²;

20 R², at each occurrence, is independently selected from

- C₁₋₄ alkyl,
- C₂₋₄ alkenyl,
- C₂₋₄ alkynyl,
- C₃₋₆ cycloalkyl,
- 25 aryl substituted with 0-5 R⁴²;
- C₃₋₁₀ carbocyclic group substituted with 0-3 R⁴¹, and

5-10 membered heterocyclic ring system containing from 1-4 heteroatoms selected from the group consisting of N, O, and S substituted with 0-3 R⁴¹;

5 R³, at each occurrence, is independently selected from H, C₁₋₄ alkyl, C₂₋₄ alkenyl, C₂₋₄ alkynyl, and C₁₋₄ alkoxy;

alternatively, R² and R³ join to form a 5- or 6-membered ring optionally substituted
10 with -O- or -N(R⁴)-;

R⁴, at each occurrence, is independently selected from H, methyl, ethyl, propyl, and butyl;

15 R⁵ is H, methyl, or ethyl;

R^{6a} is selected from

H, -OH, -NR⁴⁶R⁴⁷, -CF₃,
C₁₋₄ alkyl, C₂₋₄ alkenyl, C₂₋₄ alkynyl, C₁₋₄ alkoxy, C₁₋₄ haloalkyl, and C₃₋₆ cycloalkyl;
20

R^{6b} is H;

R⁷, R⁸, and R⁹, at each occurrence, are independently selected from
25 H, halo, -CF₃, -OCF₃, -OH, -OCH₃, -CN, -NO₂, -NR⁴⁶R⁴⁷,
C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₁₋₄ haloalkyl, C₁₋₆ alkoxy, (C₁₋₄ haloalkyl)oxy,
C₁₋₄ alkyl substituted with 0-2 R¹¹,
C₃₋₁₀ carbocyclic group substituted with 0-3 R³³,

aryl substituted with 0-5 R³³,
 5-10 membered heterocyclic ring system containing from 1-4 heteroatoms
 selected from the group consisting of N, O, and S substituted with 0-3
 R³¹;

5

OR¹², SR¹², NR¹²R¹³, C(O)H, C(O)R¹², C(O)NR¹²R¹³, NR¹⁴C(O)R¹²,
 C(O)OR¹², OC(O)R¹², CH(=NR¹⁴)NR¹²R¹³, NHC(=NR¹⁴)NR¹²R¹³,
 S(O)R¹², S(O)₂R¹², S(O)₂NR¹²R¹³, NR¹⁴S(O)₂R¹², NR¹⁴S(O)R¹²,
 NR¹⁴S(O)₂R¹², NR¹²C(O)R¹⁵, NR¹²C(O)OR¹⁵, NR¹²S(O)₂R¹⁵, and
 10 NR¹²C(O)NHR¹⁵;

R¹⁰ is selected from H, -OH, C₁₋₆ alkyl, C₁₋₄ alkoxy, and
 C₁₋₂ alkyl substituted with 0-1 R^{10B};

15 R^{10B} is C₃₋₆ cycloalkyl or
 phenyl substituted with 0-3 R³³;

R¹¹ is selected from

H, halo, -CF₃, -OCF₃, -OH, -OCH₃, -CN, -NO₂, -NR⁴⁶R⁴⁷,
 20 C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₁₋₄ haloalkyl, C₁₋₆ alkoxy, (C₁₋₄
 haloalkyl)oxy,
 C₃₋₁₀ carbocyclic group substituted with 0-3 R³³,
 aryl substituted with 0-5 R³³,
 5-10 membered heterocyclic ring system containing from 1-4 heteroatoms
 25 selected from the group consisting of N, O, and S substituted with 0-3
 R³¹;

OR¹², SR¹², NR¹²R¹³, C(O)H, C(O)R¹², C(O)NR¹²R¹³, NR¹⁴C(O)R¹²,
C(O)OR¹², OC(O)R¹², CH(=NR¹⁴)NR¹²R¹³, NHC(=NR¹⁴)NR¹²R¹³,
S(O)R¹², S(O)₂R¹², S(O)₂NR¹²R¹³, and NR¹⁴S(O)₂R¹²;

- 5 R¹², at each occurrence, is independently selected from
C₁₋₄ alkyl,
C₂₋₄ alkenyl,
C₂₋₄ alkynyl,
C₃₋₆ cycloalkyl,
10 phenyl substituted with 0-5 R³³;
C₃₋₁₀ carbocyclic group substituted with 0-3 R³³, and
5-10 membered heterocyclic ring system containing from 1-4 heteroatoms
selected from the group consisting of N, O, and S substituted with 0-3
R³¹;

- 15 R¹³, at each occurrence, is independently selected from
H, C₁₋₄ alkyl, C₂₋₄ alkenyl, and C₂₋₄ alkynyl;

- alternatively, R¹² and R¹³ join to form a 5- or 6-membered ring optionally
20 substituted with -O- or -N(R¹⁴)-;

R¹⁴, at each occurrence, is independently selected from H and C₁₋₄ alkyl;

- R³¹, at each occurrence, is independently selected from
25 H, OH, halo, CF₃, methyl, and ethyl;

R³³, at each occurrence, is independently selected from
H, OH, halo, CN, NO₂, CF₃, methyl, and ethyl;

- R^{41} , at each occurrence, is independently selected from
- H, CF_3 , halo, OH, CO_2H , SO_2R^{45} , $NR^{46}R^{47}$, NO_2 , CN, =O,
C₂₋₈ alkenyl, C₂₋₈ alkynyl, C₁₋₄ alkoxy, C₁₋₄ haloalkyl,
C₁₋₄ alkyl substituted with 0-1 R^{43} ,
5 aryl substituted with 0-3 R^{42} , and
5-10 membered heterocyclic ring system containing from 1-4 heteroatoms
selected from the group consisting of N, O, and S substituted with 0-3
 R^{44} ;
- 10 R^{42} , at each occurrence, is independently selected from
- H, CF_3 , halo, OH, CO_2H , SO_2R^{45} , SR^{45} , $NR^{46}R^{47}$, OR^{48} , NO_2 , CN,
CH(=NH)NH₂, NHC(=NH)NH₂,
C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₁₋₄ alkoxy, C₁₋₄ haloalkyl, C₃₋₆ cycloalkyl,
C₁₋₄ alkyl substituted with 0-1 R^{43} ,
15 aryl substituted with 0-3 R^{44} , and
5-10 membered heterocyclic ring system containing from 1-4 heteroatoms
selected from the group consisting of N, O, and S substituted with 0-3
 R^{44} ;
- 20 R^{43} is C₃₋₆ cycloalkyl or aryl substituted with 0-3 R^{44} ;
- R^{44} , at each occurrence, is independently selected from H, halo, -OH, $NR^{46}R^{47}$,
 CO_2H , SO_2R^{45} , - CF_3 , -OCF₃, -CN, -NO₂, C₁₋₄ alkyl, and C₁₋₄ alkoxy;
- 25 R^{45} is C₁₋₄ alkyl;

R^{46} , at each occurrence, is independently selected from H and C₁₋₃ alkyl;

R⁴⁷, at each occurrence, is independently selected from H, C₁₋₄ alkyl,
-C(=O)NH(C₁₋₄ alkyl), -SO₂(C₁₋₄ alkyl),
-SO₂(phenyl), -C(=O)O(C₁₋₄ alkyl), -C(=O)(C₁₋₄ alkyl), and -C(=O)H;

5 R⁴⁸, at each occurrence, is independently selected from H, C₁₋₄ alkyl,
-C(=O)NH(C₁₋₄ alkyl), -C(=O)O(C₁₋₄ alkyl),
-C(=O)(C₁₋₄ alkyl), and -C(=O)H;

k is 1 or 2;

10 m is 0, 1, 2; and
n is 0, 1 or 2.

In a more preferred embodiment, the present invention provides the method as
15 defined in Claim 26 where in the compound administered:

X is -CH₂-;

R¹ is selected from

20 C₂₋₄ alkyl substituted with Z,
C₂₋₄ alkenyl substituted with Z,
C₂₋₄ alkynyl substituted with Z,
C₃₋₆ cycloalkyl substituted with Z,
aryl substituted with Z,
25 5-6 membered heterocyclic ring system containing at least one heteroatom
selected from the group consisting of N, O, and S, said heterocyclic
ring system substituted with Z;
C₂₋₄ alkyl substituted with 0-2 R², and
C₂₋₄ alkenyl substituted with 0-2 R²;

30

Z is selected from H,

$$-\text{CH}(\text{OH})\text{R}^2,$$
$$-\text{C}(\text{ethylenedioxy})\text{R}^2,$$

-OR²,

5 -SR²,

$$-\text{NR}^2\text{R}^3,$$
$$-\text{C}(\text{O})\text{R}^2,$$
$$-\text{C}(\text{O})\text{NR}^2\text{R}^3,$$
$$-\text{NR}^3\text{C}(\text{O})\text{R}^2,$$

10 -C(O)OR²,

$$-\text{S}(\text{O})\text{R}^2,$$
$$-\text{S}(\text{O})_2\text{R}^2,$$
$$-\text{S}(\text{O})_2\text{NR}^2\text{R}^3, \text{ and } -\text{NR}^3\text{S}(\text{O})_2\text{R}^2;$$

15 R^2 , at each occurrence, is independently selected from

phenyl substituted with 0-5 R⁴²;

C₃₋₁₀ carbocyclic group substituted with 0-3 R⁴¹, and

5-10 membered heterocyclic ring system containing from 1-4 heteroatoms
selected from the group consisting of N, O, and S substituted with 0-3

20 R⁴¹;

R41;

\mathbf{R}^3 , at each occurrence, is independently selected from

H, C₁₋₄ alkyl, C₂₋₄ alkenyl, C₂₋₄ alkynyl, and

C₁₋₄ alkoxy;

25

alternatively, R² and R³ join to form a 5- or 6-membered ring optionally substituted with -O- or -N(R⁴)-;

with -O- or -N(R⁴)-;

R⁴, at each occurrence, is independently selected from H, methyl, ethyl, propyl, and butyl;

R⁵ is H;

5

R^{6a} is selected from H, -OH, -CF₃, methyl, ethyl, propyl, butyl, methoxy, and ethoxy;

R^{6b} is H;

10

R⁷, R⁸, and R⁹, at each occurrence, are independently selected from H, halo, -CF₃, -OCF₃, -OH, -OCH₃, -CN, -NO₂, C₁₋₄ alkyl, C₁₋₄ haloalkyl, C₁₋₄ alkoxy, (C₁₋₃ haloalkyl)oxy, and C₁₋₄ alkyl substituted with 0-2 R¹¹;

15

R¹¹ is selected from H, halo, -CF₃, -OCF₃, -OH, -OCH₃, -CN, -NO₂, C₁₋₄ alkyl, C₁₋₄ haloalkyl, C₁₋₄ alkoxy, and (C₁₋₃ haloalkyl)oxy;

20 R³³, at each occurrence, is independently selected from H, OH, halo, CF₃, and methyl;

R⁴¹, at each occurrence, is independently selected from H, CF₃, halo, OH, CO₂H, SO₂R⁴⁵, NR⁴⁶R⁴⁷, NO₂, CN, =O, C₂₋₈ alkenyl, C₂₋₈ alkynyl, C₁₋₄ alkoxy, C₁₋₄ haloalkyl, C₁₋₄ alkyl substituted with 0-1 R⁴³, aryl substituted with 0-3 R⁴², and

25

5-10 membered heterocyclic ring system containing from 1-4 heteroatoms selected from the group consisting of N, O, and S substituted with 0-3 R⁴⁴;

- 5 R⁴², at each occurrence, is independently selected from
H, CF₃, halo, OH, CO₂H, SO₂R⁴⁵, SR⁴⁵, NR⁴⁶R⁴⁷, OR⁴⁸, NO₂, CN,
CH(=NH)NH₂, NHC(=NH)NH₂,
C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₁₋₄ alkoxy, C₁₋₄ haloalkyl, C₃₋₆ cycloalkyl,
C₁₋₄ alkyl substituted with 0-1 R⁴³,
10 aryl substituted with 0-3 R⁴⁴, and
5-10 membered heterocyclic ring system containing from 1-4 heteroatoms
selected from the group consisting of N, O, and S substituted with 0-3
R⁴⁴;
- 15 R⁴³ is cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, phenyl, or pyridyl, each
substituted with 0-3 R⁴⁴;

- R⁴⁴, at each occurrence, is independently selected from H, halo, -OH, NR⁴⁶R⁴⁷,
CO₂H, SO₂R⁴⁵, -CF₃, -OCF₃, -CN, -NO₂, methyl, ethyl, propyl, butyl,
20 methoxy, ethoxy, propoxy, and butoxy;

R⁴⁵ is methyl, ethyl, propyl, or butyl;

- R⁴⁶, at each occurrence, is independently selected from H, methyl, ethyl, propyl, and
25 butyl;

R⁴⁷, at each occurrence, is independently selected from
H, methyl, ethyl, n-propyl, i-propyl, n-butyl,
i-butyl, -C(=O)NH(methyl), -C(=O)NH(ethyl),

-SO₂(methyl), -SO₂(ethyl), -SO₂(phenyl),
-C(=O)O(methyl), -C(=O)O(ethyl), -C(=O)(methyl),
-C(=O)(ethyl), and -C(=O)H;

5 R⁴⁸, at each occurrence, is independently selected from

H, methyl, ethyl, n-propyl, i-propyl, -C(=O)NH(methyl), -C(=O)NH(ethyl), -
C(=O)O(methyl), -C(=O)O(ethyl), -C(=O)(methyl), -C(=O)(ethyl), and
-C(=O)H;

10 k is 1;

m is 0, 1, or 2; and

n is 0, 1 or 2.

15 In a more preferred embodiment, the present invention provides the method as
defined in Claim 26 where in the compound administered:

X is -CH₂-;

20 R¹ is selected from

ethyl substituted with Z,

propyl substituted with Z,

butyl substituted with Z,

propenyl substituted with Z,

25 butenyl substituted with Z,

ethyl substituted with R²,

propyl substituted with R²,

butyl substituted with R²,

propenyl substituted with R², and

30 butenyl substituted with R²;

Z is selected from H,

- CH(OH)R²,
- OR²,
- 5 -SR²,
- NR²R³,
- C(O)R²,
- C(O)NR²R³,
- NR³C(O)R²,
- 10 -C(O)OR²,
- S(O)R²,
- S(O)₂R²,
- S(O)₂NR²R³, and -NR³S(O)₂R²;

15 R², at each occurrence, is independently selected from

- phenyl substituted with 0-3 R⁴²;
- naphthyl substituted with 0-3 R⁴²;
- cyclopropyl substituted with 0-3 R⁴¹;
- cyclobutyl substituted with 0-3 R⁴¹;
- 20 cyclopentyl substituted with 0-3 R⁴¹;
- cyclohexyl substituted with 0-3 R⁴¹;
- pyridyl substituted with 0-3 R⁴¹;
- indolyl substituted with 0-3 R⁴¹;
- indolinyl substituted with 0-3 R⁴¹;
- 25 benzimidazolyl substituted with 0-3 R⁴¹;
- benzotriazolyl substituted with 0-3 R⁴¹;
- benzothienyl substituted with 0-3 R⁴¹;
- benzofuranyl substituted with 0-3 R⁴¹;

phthalimid-1-yl substituted with 0-3 R⁴¹;
inden-2-yl substituted with 0-3 R⁴¹;
2,3-dihydro-1H-inden-2-yl substituted with 0-3 R⁴¹;
indazolyl substituted with 0-3 R⁴¹;
5 tetrahydroquinolinyl substituted with 0-3 R⁴¹; and
tetrahydro-isoquinolinyl substituted with 0-3 R⁴¹;

R³, at each occurrence, is independently selected from
H, methyl, and ethyl;

10

R⁵ is H;

R^{6a} is selected from H, -OH, methyl, and methoxy;

15 R^{6b} is H;

R⁷, R⁸, and R⁹, at each occurrence, are independently selected from H, F, Cl, methyl,
ethyl, methoxy, -CF₃,
and -OCF₃;

20

R⁴¹, at each occurrence, is independently selected from
H, F, Cl, Br, OH, CF₃, NO₂, CN, =O, methyl, ethyl, propyl, butyl, methoxy,
and ethoxy;

25 R⁴², at each occurrence, is independently selected from
H, F, Cl, Br, OH, CF₃, SO₂R⁴⁵, SR⁴⁵, NR⁴⁶R⁴⁷, OR⁴⁸, NO₂, CN, =O,
methyl, ethyl, propyl, butyl, methoxy, and ethoxy;

R⁴⁵ is methyl, ethyl, propyl, or butyl;

R⁴⁶, at each occurrence, is independently selected from H, methyl, ethyl, propyl, and butyl;

5 R⁴⁷, at each occurrence, is independently selected from
H, methyl, ethyl, n-propyl, i-propyl, n-butyl,
i-butyl, -C(=O)NH(methyl), -C(=O)NH(ethyl),
-SO₂(methyl), -SO₂(ethyl), -SO₂(phenyl),
-C(=O)O(methyl), -C(=O)O(ethyl), -C(=O)(methyl),
10 -C(=O)(ethyl), and -C(=O)H;

R⁴⁸, at each occurrence, is independently selected from
H, methyl, ethyl, n-propyl, i-propyl, -C(=O)NH(methyl), -C(=O)NH(ethyl), -
C(=O)O(methyl), -C(=O)O(ethyl), -C(=O)(methyl), -C(=O)(ethyl), and
15 -C(=O)H;

k is 1;

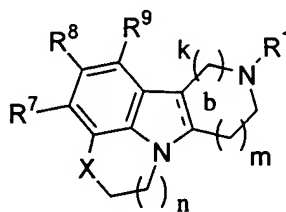
m is 0, 1, or 2; and

n is 0, 1 or 2.

20

In a more preferred embodiment, the present invention provides the method as defined in Claim 26 where the compound administered is a compound of Formula (I-a):

25



(I-a)

wherein:

b is a single bond;

5 X is -CH₂-, CH(OH)-, or -C(=O)-

R¹ is selected from

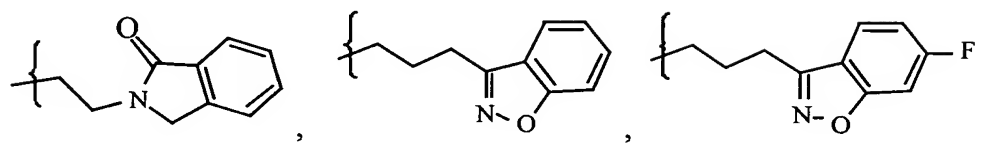
- (CH₂)₃C(=O)(4-fluoro-phenyl),
- (CH₂)₃C(=O)(4-bromo-phenyl),
- 10 - (CH₂)₃C(=O)(4-methyl-phenyl),
- (CH₂)₃C(=O)(4-methoxy-phenyl),
- (CH₂)₃C(=O)(4-(3,4-dichloro-phenyl)phenyl),
- (CH₂)₃C(=O)(3-methyl-4-fluoro-phenyl),
- (CH₂)₃C(=O)(2,3-dimethoxy-phenyl),
- 15 - (CH₂)₃C(=O)(phenyl),
- (CH₂)₃C(=O)(4-chloro-phenyl),
- (CH₂)₃C(=O)(3-methyl-phenyl),
- (CH₂)₃C(=O)(4-t-butyl-phenyl),
- (CH₂)₃C(=O)(3,4-difluoro-phenyl),
- 20 - (CH₂)₃C(=O)(2-methoxy-5-fluoro-phenyl),
- (CH₂)₃C(=O)(4-fluoro-1-naphthyl),
- (CH₂)₃C(=O)(benzyl),
- (CH₂)₃C(=O)(4-pyridyl),
- (CH₂)₃C(=O)(3-pyridyl),
- 25 - (CH₂)₃CH(OH)(4-fluoro-phenyl),
- (CH₂)₃CH(OH)(4-pyridyl),
- (CH₂)₃CH(OH)(2,3-dimethoxy-phenyl),
- (CH₂)₃S(3-fluoro-phenyl),
- (CH₂)₃S(4-fluoro-phenyl),

- (CH₂)₃S(=O)(4-fluoro-phenyl),
- (CH₂)₃SO₂(3-fluoro-phenyl),
- (CH₂)₃SO₂(4-fluoro-phenyl),
- (CH₂)₃O(4-fluoro-phenyl),
- 5 - (CH₂)₃O(phenyl),
- (CH₂)₃O(3-pyridyl),
- (CH₂)₃O(4-pyridyl),
- (CH₂)₃O(2-NH₂-phenyl),
- (CH₂)₃O(2-NH₂-5-F-phenyl),
- 10 - (CH₂)₃O(2-NH₂-4-F-phenyl),
- (CH₂)₃O(2-NH₂-3-F-phenyl),
- (CH₂)₃O(2-NH₂-4-Cl-phenyl),
- (CH₂)₃O(2-NH₂-4-OH-phenyl),
- (CH₂)₃O(2-NH₂-4-Br-phenyl),
- 15 - (CH₂)₃O(2-NHC(=O)Me-4-F-phenyl),
- (CH₂)₃O(2-NHC(=O)Me-phenyl),
- (CH₂)₃NH(4-fluoro-phenyl),
- (CH₂)₃N(methyl)(4-fluoro-phenyl),
- (CH₂)₃CO₂(ethyl),
- 20 - (CH₂)₃C(=O)N(methyl)(methoxy),
- (CH₂)₃C(=O)NH(4-fluoro-phenyl),
- (CH₂)₂NHC(=O)(phenyl),
- (CH₂)₂NMeC(=O)(phenyl),
- (CH₂)₂NHC(=O)(2-fluoro-phenyl),
- 25 - (CH₂)₂NMeC(=O)(2-fluoro-phenyl),
- (CH₂)₂NHC(=O)(4-fluoro-phenyl),
- (CH₂)₂NMeC(=O)(4-fluoro-phenyl),
- (CH₂)₂NHC(=O)(2,4-difluoro-phenyl),
- (CH₂)₂NMeC(=O)(2,4-difluoro-phenyl),

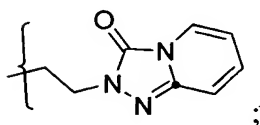
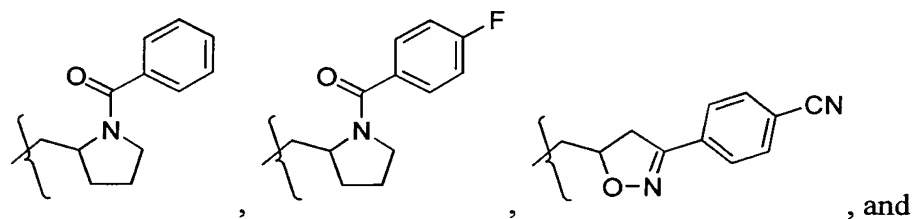
- (CH₂)₃(3-indolyl),
- (CH₂)₃(1-methyl-3-indolyl),
- (CH₂)₃(1-indolyl),
- (CH₂)₃(1-indoliny),
- 5 - (CH₂)₃(1-benzimidazolyl),
- (CH₂)₃(1H-1,2,3-benzotriazol-1-yl),
- (CH₂)₃(1H-1,2,3-benzotriazol-2-yl),
- (CH₂)₂(1H-1,2,3-benzotriazol-1-yl),
- (CH₂)₂(1H-1,2,3-benzotriazol-2-yl),
- 10 - (CH₂)₃(3,4 dihydro-1(2H)-quinoliny),
- (CH₂)₂C(=O)(4-fluoro-phenyl),
- (CH₂)₂C(=O)NH(4-fluoro-phenyl),
- CH₂CH₂(3-indolyl),
- CH₂CH₂(1-phthalimidyl),
- 15 - (CH₂)₄C(=O)N(methyl)(methoxy),
- (CH₂)₄CO₂(ethyl),
- (CH₂)₄C(=O)(phenyl),
- (CH₂)₄(cyclohexyl),
- (CH₂)₃CH(phenyl)₂,
- 20 - CH₂CH₂CH=C(phenyl)₂,
- CH₂CH₂CH=CMe(4-F-phenyl),
- (CH₂)₃CH(4-fluoro-phenyl)₂,
- CH₂CH₂CH=C(4-fluoro-phenyl)₂,
- (CH₂)₂(2,3-dihydro-1H-inden-2-yl),
- 25 - (CH₂)₃C(=O)(2-NH₂-phenyl),
- (CH₂)₃C(=O)(2-NH₂-5-F-phenyl),
- (CH₂)₃C(=O)(2-NH₂-4-F-phenyl),
- (CH₂)₃C(=O)(2-NH₂-3-F-phenyl),
- (CH₂)₃C(=O)(2-NH₂-4-Cl-phenyl),

- (CH₂)₃C(=O)(2-NH₂-4-OH-phenyl),
- (CH₂)₃C(=O)(2-NH₂-4-Br-phenyl),
- (CH₂)₃(1H-indazol-3-yl),
- (CH₂)₃(5-F-1H-indazol-3-yl),
- 5 - (CH₂)₃(7-F-1H-indazol-3-yl),
- (CH₂)₃(6-Cl-1H-indazol-3-yl),
- (CH₂)₃(6-Br-1H-indazol-3-yl),
- (CH₂)₃C(=O)(2-NHMe-phenyl),
- (CH₂)₃(1-benzothien-3-yl),
- 10 - (CH₂)₃(6-F-1H-indol-1-yl),
- (CH₂)₃(5-F-1H-indol-1-yl),
- (CH₂)₃(6-F-2,3-dihydro-1H-indol-1-yl),
- (CH₂)₃(5-F-2,3-dihydro-1H-indol-1-yl),
- (CH₂)₃(6-F-1H-indol-3-yl),
- 15 - (CH₂)₃(5-F-1H-indol-3-yl),
- (CH₂)₃(5-F-1H-indol-3-yl),
- (CH₂)₃(9H-purin-9-yl),
- (CH₂)₃(7H-purin-7-yl),
- (CH₂)₃(6-F-1H-indazol-3-yl),
- 20 - (CH₂)₃C(=O)(2-NHSO₂Me-4-F-phenyl),
- (CH₂)₃C(=O)(2-NHC(=O)Me-4-F-phenyl),
- (CH₂)₃C(=O)(2-NHC(=O)Me-phenyl),
- (CH₂)₃C(=O)(2-NHCO₂Et-4-F-phenyl),
- (CH₂)₃C(=O)(2-NHC(=O)NEt-4-F-phenyl),
- 25 - (CH₂)₃C(=O)(2-NHCHO-4-F-phenyl),
- (CH₂)₃C(=O)(2-OH-4-F-phenyl),
- (CH₂)₃C(=O)(2-MeS-4-F-phenyl),
- (CH₂)₃C(=O)(2-NHSO₂Me-4-F-phenyl),
- (CH₂)₂C(Me)CO₂Me,

$-(\text{CH}_2)_2\text{C}(\text{Me})\text{CH}(\text{OH})(4\text{-F-phenyl})_2$,
 $-(\text{CH}_2)_2\text{C}(\text{Me})\text{CH}(\text{OH})(4\text{-Cl-phenyl})_2$,
 $-(\text{CH}_2)_2\text{C}(\text{Me})\text{C}(=\text{O})(4\text{-F-phenyl})$,
 $-(\text{CH}_2)_2\text{C}(\text{Me})\text{C}(=\text{O})(2\text{-MeO-4-F-phenyl})$,
5 $-(\text{CH}_2)_2\text{C}(\text{Me})\text{C}(=\text{O})(3\text{-Me-4-F-phenyl})$,
 $-(\text{CH}_2)_2\text{C}(\text{Me})\text{C}(=\text{O})(2\text{-Me-phenyl})$,
 $-(\text{CH}_2)_2\text{C}(\text{Me})\text{C}(=\text{O})\text{phenyl}$,



10



- 15 R^7 , R^8 , and R^9 , at each occurrence, are independently selected from
 hydrogen, fluoro, chloro, bromo, cyano, methyl, ethyl, propyl, isopropyl, butyl,
 t-butyl, nitro, trifluoromethyl, methoxy, ethoxy, isopropoxy, trifluoromethoxy,
 phenyl, benzyl,
- 20 $\text{HC}(=\text{O})$ -, $\text{methylC}(=\text{O})$ -, $\text{ethylC}(=\text{O})$ -, $\text{propylC}(=\text{O})$ -, $\text{isopropylC}(=\text{O})$ -, n-
 $\text{butylC}(=\text{O})$ -, $\text{isobutylC}(=\text{O})$ -, $\text{secbutylC}(=\text{O})$ -, $\text{tertbutylC}(=\text{O})$ -, $\text{phenylC}(=\text{O})$ -,

methylC(=O)NH-, ethylC(=O)NH -, propylC(=O)NH-, isopropylC(=O)NH-,
n-butylC(=O)NH-, isobutylC(=O)NH-, secbutylC(=O)NH-,
tertbutylC(=O)NH-, phenylC(=O)NH-,

5 methylamino-, ethylamino-, propylamino-, isopropylamino-, n-butylamino-,
isobutylamino-, secbutylamino-, tertbutylamino-, phenylamino-,

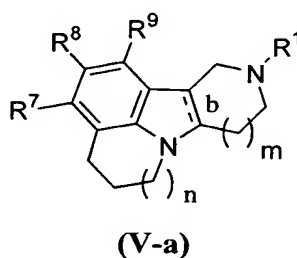
provided that two of substituents R⁷, R⁸, and R⁹, are independently selected
from hydrogen, fluoro, chloro, bromo, cyano, methyl, ethyl, propyl, isopropyl,
10 butyl, t-butyl, nitro, trifluoromethyl, methoxy, ethoxy, isopropoxy, and
trifluoromethoxy;

k is 1 or 2;

m is 1 or 2; and

15 n is 0, 1 or 2.

In a more preferred embodiment, the present invention provides the method as
defined in Claim 30 where the compound administered is a compound of Formula (V-
20 a):



25 wherein:

b is a single bond, wherein the bridge hydrogens are in a cis position;

R¹ is selected from

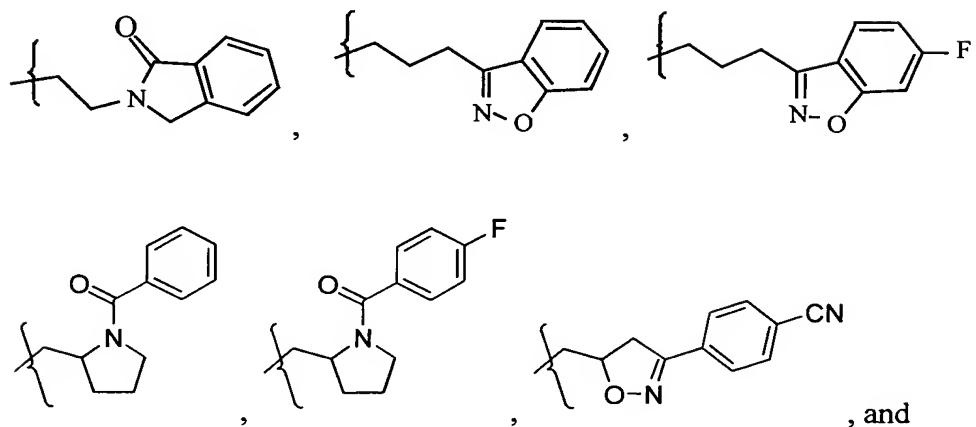
- (CH₂)₃C(=O)(4-fluoro-phenyl),
- (CH₂)₃C(=O)(4-bromo-phenyl),
- (CH₂)₃C(=O)(4-methyl-phenyl),
- 5 - (CH₂)₃C(=O)(4-methoxy-phenyl),
- (CH₂)₃C(=O)(4-(3,4-dichloro-phenyl)phenyl),
- (CH₂)₃C(=O)(3-methyl-4-fluoro-phenyl),
- (CH₂)₃C(=O)(2,3-dimethoxy-phenyl),
- (CH₂)₃C(=O)(phenyl),
- 10 - (CH₂)₃C(=O)(4-chloro-phenyl),
- (CH₂)₃C(=O)(3-methyl-phenyl),
- (CH₂)₃C(=O)(4-t-butyl-phenyl),
- (CH₂)₃C(=O)(3,4-difluoro-phenyl),
- (CH₂)₃C(=O)(2-methoxy-5-fluoro-phenyl),
- 15 - (CH₂)₃C(=O)(4-fluoro-1-naphthyl),
- (CH₂)₃C(=O)(benzyl),
- (CH₂)₃C(=O)(4-pyridyl),
- (CH₂)₃C(=O)(3-pyridyl),
- (CH₂)₃CH(OH)(4-fluoro-phenyl),
- 20 - (CH₂)₃CH(OH)(4-pyridyl),
- (CH₂)₃CH(OH)(2,3-dimethoxy-phenyl),
- (CH₂)₃S(3-fluoro-phenyl),
- (CH₂)₃S(4-fluoro-phenyl),
- (CH₂)₃S(=O)(4-fluoro-phenyl),
- 25 - (CH₂)₃SO₂(3-fluoro-phenyl),
- (CH₂)₃SO₂(4-fluoro-phenyl),
- (CH₂)₃O(4-fluoro-phenyl),
- (CH₂)₃O(phenyl) ,
- (CH₂)₃NH(4-fluoro-phenyl),

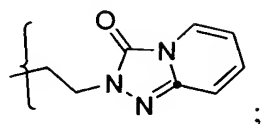
- (CH₂)₃N(methyl)(4-fluoro-phenyl),
- (CH₂)₃CO₂(ethyl),
- (CH₂)₃C(=O)N(methyl)(methoxy),
- (CH₂)₃C(=O)NH(4-fluoro-phenyl),
- 5 - (CH₂)₂NHC(=O)(phenyl),
- (CH₂)₂NMeC(=O)(phenyl),
- (CH₂)₂NHC(=O)(2-fluoro-phenyl),
- (CH₂)₂NMeC(=O)(2-fluoro-phenyl),
- (CH₂)₂NHC(=O)(4-fluoro-phenyl),
- 10 - (CH₂)₂NMeC(=O)(4-fluoro-phenyl),
- (CH₂)₂NHC(=O)(2,4-difluoro-phenyl),
- (CH₂)₂NMeC(=O)(2,4-difluoro-phenyl),
- (CH₂)₃(3-indolyl),
- (CH₂)₃(1-methyl-3-indolyl),
- 15 - (CH₂)₃(1-indolyl),
- (CH₂)₃(1-indolyl),
- (CH₂)₃(1-benzimidazolyl),
- (CH₂)₃(1H-1,2,3-benzotriazol-1-yl),
- (CH₂)₃(1H-1,2,3-benzotriazol-2-yl),
- 20 - (CH₂)₂(1H-1,2,3-benzotriazol-1-yl),
- (CH₂)₂(1H-1,2,3-benzotriazol-2-yl),
- (CH₂)₃(3,4 dihydro-1(2H)-quinolyl),
- (CH₂)₂C(=O)(4-fluoro-phenyl),
- (CH₂)₂C(=O)NH(4-fluoro-phenyl),
- 25 - CH₂CH₂(3-indolyl),
- CH₂CH₂(1-phthalimidyl),
- (CH₂)₄C(=O)N(methyl)(methoxy),
- (CH₂)₄CO₂(ethyl),
- (CH₂)₄C(=O)(phenyl),

- (CH₂)₄(cyclohexyl),
- (CH₂)₃CH(phenyl)₂,
- CH₂CH₂CH=C(phenyl)₂,
- CH₂CH₂CH=CMe(4-F-phenyl),
- 5 -(CH₂)₃CH(4-fluoro-phenyl)₂,
- CH₂CH₂CH=C(4-fluoro-phenyl)₂,
- (CH₂)₂(2,3-dihydro-1H-inden-2-yl),
- (CH₂)₃C(=O)(2-NH₂-phenyl),
- (CH₂)₃C(=O)(2-NH₂-5-F-phenyl),
- 10 -(CH₂)₃C(=O)(2-NH₂-4-F-phenyl),
- (CH₂)₃C(=O)(2-NH₂-3-F-phenyl),
- (CH₂)₃C(=O)(2-NH₂-4-Cl-phenyl),
- (CH₂)₃C(=O)(2-NH₂-4-OH-phenyl),
- (CH₂)₃C(=O)(2-NH₂-4-Br-phenyl),
- 15 -(CH₂)₃(1H-indazol-3-yl),
- (CH₂)₃(5-F-1H-indazol-3-yl),
- (CH₂)₃(7-F-1H-indazol-3-yl),
- (CH₂)₃(6-Cl-1H-indazol-3-yl),
- (CH₂)₃(6-Br-1H-indazol-3-yl),
- 20 -(CH₂)₃C(=O)(2-NHMe-phenyl),
- (CH₂)₃(1-benzothien-3-yl),
- (CH₂)₃(6-F-1H-indol-1-yl),
- (CH₂)₃(5-F-1H-indol-1-yl),
- (CH₂)₃(6-F-2,3-dihydro-1H-indol-1-yl),
- 25 -(CH₂)₃(5-F-2,3-dihydro-1H-indol-1-yl),
- (CH₂)₃(6-F-1H-indol-3-yl),
- (CH₂)₃(5-F-1H-indol-3-yl),
- (CH₂)₃(5-F-1H-indol-3-yl),
- (CH₂)₃(9H-purin-9-yl),

- (CH₂)₃(7H-purin-7-yl),
 -(CH₂)₃(6-F-1H-indazol-3-yl),
 -(CH₂)₃C(=O)(2-NHSO₂Me-4-F-phenyl),
 -(CH₂)₃C(=O)(2-NHC(=O)Me-4-F-phenyl),
 5 -(CH₂)₃C(=O)(2-NHC(=O)Me-4-F-phenyl),
 -(CH₂)₃C(=O)(2-NHCO₂Et-4-F-phenyl),
 -(CH₂)₃C(=O)(2-NHC(=O)NH₂-4-F-phenyl),
 -(CH₂)₃C(=O)(2-NHCHO-4-F-phenyl),
 -(CH₂)₃C(=O)(2-OH-4-F-phenyl),
 10 -(CH₂)₃C(=O)(2-MeS-4-F-phenyl),
 -(CH₂)₃C(=O)(2-NHSO₂Me-4-F-phenyl),
 -(CH₂)₂C(Me)CO₂Me,
 -(CH₂)₂C(Me)CH(OH)(4-F-phenyl)₂,
 -(CH₂)₂C(Me)CH(OH)(4-Cl-phenyl)₂,
 15 -(CH₂)₂C(Me)C(=O)(4-F-phenyl),
 -(CH₂)₂C(Me)C(=O)(2-MeO-4-F-phenyl),
 -(CH₂)₂C(Me)C(=O)(3-Me-4-F-phenyl),
 -(CH₂)₂C(Me)C(=O)(2-Me-phenyl),
 -(CH₂)₂C(Me)C(=O)phenyl,

20





5 R⁷, R⁸, and R⁹, at each occurrence, are independently selected from hydrogen, fluoro, chloro, bromo, cyano, methyl, ethyl, propyl, isopropyl, butyl, t-butyl, nitro, trifluoromethyl, methoxy, ethoxy, isopropoxy, trifluoromethoxy, methylC(=O)-, ethylC(=O)-, propylC(=O)-, isopropylC(=O)-, methylC(=O)NH-, ethylC(=O)NH -, propylC(=O)NH-, isopropylC(=O)NH, methylamino-, ethylamino-, propylamino-, and isopropylamino-,

10 provided that two of substituents R⁷, R⁸, and R⁹, are independently selected from hydrogen, fluoro, chloro, methyl, trifluoromethyl, methoxy, and trifluoromethoxy;

m is 1 or 2; and

15 n is 0, 1 or 2.

In a more preferred embodiment, the present invention provides the method as defined in Claim 18 where the compound administered is selected from the group:

20 (±)-*cis*-9-(cyclopropylcarbonyl)-4,5,6a,7,8,9,10,10a-octahydropyrido[4,3-*b*]pyrrolo[3,2,1-*hi*]indole;

25 (±)-*cis*-9-isobutyryl-4,5,6a,7,8,9,10,10a-octahydropyrido[4,3-*b*]pyrrolo[3,2,1-*hi*]indole;

tert-butyl (±)-*cis*-2-(2-chlorophenyl)-4,5,7,8,10,10a-hexahydropyrido[4,3-*b*]pyrrolo[3,2,1-*hi*]indole-9(6a*H*)-carboxylate;

- tert*-butyl (±)-*cis*-2-(2,4-dichlorophenyl)-4,5,7,8,10,10a-hexahydropyrido[4,3-*b*]pyrrolo[3,2,1-*hi*]indole-9(6a*H*)-carboxylate;
- 5 *tert*-butyl (±)-*cis*-2-(3,4-dichlorophenyl)-4,5,7,8,10,10a-hexahydropyrido[4,3-*b*]pyrrolo[3,2,1-*hi*]indole-9(6a*H*)-carboxylate;
- tert*-butyl (±)-*cis*-2-(2,3-dichlorophenyl)-4,5,7,8,10,10a-hexahydropyrido[4,3-*b*]pyrrolo[3,2,1-*hi*]indole-9(6a*H*)-carboxylate;
- 10 *tert*-butyl (±)-*cis*-2-[2-chloro-4-(trifluoromethyl)phenyl]-4,5,7,8,10,10a-hexahydropyrido[4,3-*b*]pyrrolo[3,2,1-*hi*]indole-9(6a*H*)-carboxylate;
- tert*-butyl (±)-*cis*-2-(2-chloro-4-methoxyphenyl)-4,5,7,8,10,10a-hexahydropyrido[4,3-*b*]pyrrolo[3,2,1-*hi*]indole-9(6a*H*)-carboxylate;
- 15 *tert*-butyl (±)-*cis*-2-(5-isopropyl-2-methoxyphenyl)-4,5,7,8,10,10a-hexahydropyrido[4,3-*b*]pyrrolo[3,2,1-*hi*]indole-9(6a*H*)-carboxylate;
- tert*-butyl (±)-*cis*-2-(3-fluorophenyl)-4,5,7,8,10,10a-hexahydropyrido[4,3-*b*]pyrrolo[3,2,1-*hi*]indole-9(6a*H*)-carboxylate;
- 20 *tert*-butyl (±)-*cis*-2-(2,4-dimethoxyphenyl)-4,5,7,8,10,10a-hexahydropyrido[4,3-*b*]pyrrolo[3,2,1-*hi*]indole-9(6a*H*)-carboxylate;
- (±)-*cis*-2-(2-chlorophenyl)-4,5,6a,7,8,9,10,10a-octahydropyrido[4,3-*b*]pyrrolo[3,2,1-*hi*]indole;
- 25 (±)-*cis*-2-(2,4-dichlorophenyl)-4,5,6a,7,8,9,10,10a-octahydropyrido[4,3-*b*]pyrrolo[3,2,1-*hi*]indole;
- 30 (±)-*cis*-2-(3,4-dichlorophenyl)-4,5,6a,7,8,9,10,10a-octahydropyrido[4,3-*b*]pyrrolo[3,2,1-*hi*]indole;

- (±)-*cis*-2-(2,3-dichlorophenyl)-4,5,6a,7,8,9,10,10a-octahydropyrido[4,3-*b*]pyrrolo[3,2,1-*hi*]indole;
- 5 (±)-*cis*-2-[2-chloro-4-(trifluoromethyl)phenyl]-4,5,6a,7,8,9,10,10a-octahydropyrido[4,3-*b*]pyrrolo[3,2,1-*hi*]indole;
- (±)-*cis*-2-(2-chloro-4-methoxyphenyl)-4,5,6a,7,8,9,10,10a-octahydropyrido[4,3-*b*]pyrrolo[3,2,1-*hi*]indole;
- 10 (±)-*cis*-2-(4-isopropyl-2-methoxyphenyl)-4,5,6a,7,8,9,10,10a-octahydropyrido[4,3-*b*]pyrrolo[3,2,1-*hi*]indole;
- (±)-*cis*-2-(3-fluorophenyl)-4,5,6a,7,8,9,10,10a-octahydropyrido[4,3-*b*]pyrrolo[3,2,1-*hi*]indole;
- 15 (±)-*cis*-2-(2,4-dimethoxyphenyl)-4,5,6a,7,8,9,10,10a-octahydropyrido[4,3-*b*]pyrrolo[3,2,1-*hi*]indole;
- 20 *tert*-butyl (±)-*cis*-5,6,8,9,11,11a-hexahydro-4*H*-pyrido[3',4':4,5]pyrrolo[3,2,1-*ij*]quinoline-10(7*aH*)-carboxylate;
- tert*-butyl (±)-*cis*-2-bromo-5,6,8,9,11,11a-hexahydro-4*H*-pyrido[3',4':4,5]pyrrolo[3,2,1-*ij*]quinoline-10(7*aH*)-carboxylate;
- 25 *tert*-butyl (±)-*cis*-2-(2,3-dichlorophenyl)-5,6,8,9,11,11a-hexahydro-4*H*-pyrido[3',4':4,5]pyrrolo[3,2,1-*ij*]quinoline-10(7*aH*)-carboxylate;
- tert*-butyl (±)-*cis*-2-(3,4-dichlorophenyl)-5,6,8,9,11,11a-hexahydro-4*H*-pyrido[3',4':4,5]pyrrolo[3,2,1-*ij*]quinoline-10(7*aH*)-carboxylate;
- 30

tert-butyl (±)-*cis*-2-[2-chloro-4-(trifluoromethyl)phenyl]-5,6,8,9,11,11a-hexahydro-4*H*-pyrido[3',4':4,5]pyrrolo[3,2,1-*ij*]quinoline-10(7*aH*)-carboxylate;

5 (±)-*cis*-2-(2,3-dichlorophenyl)-5,6,7a,8,9,10,11,11a-octahydro-4*H*-pyrido[3',4':4,5]pyrrolo[3,2,1-*ij*]quinoline;

(±)-*cis*-2-(3,4-dichlorophenyl)-5,6,7a,8,9,10,11,11a-octahydro-4*H*-pyrido[3',4':4,5]pyrrolo[3,2,1-*ij*]quinoline;

10

(±)-*cis*-2-[2-chloro-4-(trifluoromethyl)phenyl]-5,6,7a,8,9,10,11,11a-octahydro-4*H*-pyrido[3',4':4,5]pyrrolo[3,2,1-*ij*]quinoline;

15

4-((±)-*cis*-2-(2-chlorophenyl)-4,5,7,8,10,10a-hexahydropyrido[4,3-*b*]pyrrolo[3,2,1-*hi*]indol-9(6*aH*)-yl)-1-(4-fluorophenyl)-1-butanone;

4-((±)-*cis*-2-(2,4-dichlorophenyl)-4,5,7,8,10,10a-hexahydropyrido[4,3-*b*]pyrrolo[3,2,1-*hi*]indol-9(6*aH*)-yl)-1-(4-fluorophenyl)-1-butanone;

20

4-((±)-*cis*-5,6,8,9,11,11a-hexahydro-4*H*-pyrido[3',4':4,5]pyrrolo[3,2,1-*ij*]quinolin-10(7*aH*)-yl)-1-(4-fluorophenyl)-1-butanone;

4-((±)-*cis*-4,5,7,8,10,10a-hexahydropyrido[4,3-*b*]pyrrolo[3,2,1-*hi*]indol-9(6*aH*)-yl)-1-(4-fluorophenyl)-1-butanone;

25

(6*aS*,10*aR*)-2-(2-fluoro-4-methoxyphenyl)-4,5,6a,7,8,9,10,10a-octahydropyrido[4,3-*b*]pyrrolo[3,2,1-*hi*]indole;

30

tert-butyl (6*aS*,10*aR*)-2-[4-ethoxy-2-(trifluoromethyl)phenyl]-4,5,7,8,10,10a-hexahydropyrido[4,3-*b*]pyrrolo[3,2,1-*hi*]indole-9(6*aH*)-carboxylate;

- (6a*S*,10a*R*)-2-[4-ethoxy-2-(trifluoromethyl)phenyl]-4,5,6a,7,8,9,10,10a-octahydropyrido [4,3-*b*]pyrrolo[3,2,1-*hi*]indole;
- 5 *tert*-butyl (6a*S*,10a*R*)-2-(4-chloro-2-fluorophenyl)-4,5,7,8,10,10a-hexahydropyrido[4,3-*b*]pyrrolo[3,2,1-*hi*]indole-9(6a*H*)-carboxylate;
- (6a*S*,10a*R*)- 2-(4-chloro-2-fluorophenyl)-4,5,6a,7,8,9,10,10a-octahydropyrido [4,3-*b*]pyrrolo[3,2,1-*hi*]indole;
- 10 *tert*-butyl (6a*S*,10a*R*)-2-[4-isopropoxy-2-(trifluoromethyl)phenyl]-4,5,7,8,10,10a-hexahydropyrido[4,3-*b*]pyrrolo[3,2,1-*hi*]indole-9(6a*H*)-carboxylate;
- (6a*S*,10a*R*)-2-[4-isopropoxy-2-(trifluoromethyl)phenyl]-4,5,6a,7,8,9,10,10a-octahydropyrido [4,3-*b*]pyrrolo[3,2,1-*hi*]indole;
- 15 *tert*-butyl (6a*S*,10a*R*)-2-[4-methoxy-2-(trifluoromethyl)phenyl]-4,5,7,8,10,10a-hexahydropyrido[4,3-*b*]pyrrolo[3,2,1-*hi*]indole-9(6a*H*)-carboxylate;
- (6a*S*,10a*R*)-2-[4-methoxy-2-(trifluoromethyl)phenyl]-4,5,6a,7,8,9,10,10a-octahydropyrido [4,3-*b*]pyrrolo[3,2,1-*hi*]indole;
- 20 *tert*-butyl (6a*S*,10a*R*)-2-phenyl-4,5,7,8,10,10a-hexahydropyrido[4,3-*b*]pyrrolo[3,2,1-*hi*]indole-9(6a*H*)-carboxylate;
- 25 (6a*S*,10a*R*)-2-phenyl-4,5,6a,7,8,9,10,10a-octahydropyrido [4,3-*b*]pyrrolo[3,2,1-*hi*]indole;
- tert*-butyl (6a*S*,10a*R*)-2-(2-methylphenyl)-4,5,7,8,10,10a-hexahydropyrido[4,3-*b*]pyrrolo[3,2,1-*hi*]indole-9(6a*H*)-carboxylate;
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(6a*S*,10a*R*)-2-(2-methylphenyl)-4,5,6a,7,8,9,10,10a-octahydropyrido [4,3-*b*]pyrrolo[3,2,1-*hi*]indole;

5 *tert*-butyl (6a*S*,10a*R*)-2-[2-(trifluoromethyl)phenyl]-4,5,7,8,10,10a-hexahydropyrido[4,3-*b*]pyrrolo[3,2,1-*hi*]indole-9(6a*H*)-carboxylate;

(6a*S*,10a*R*)-2-[2-(trifluoromethyl)phenyl]-4,5,6a,7,8,9,10,10a-octahydropyrido [4,3-*b*]pyrrolo[3,2,1-*hi*]indole;

10 *tert*-butyl (6a*S*,10a*R*)-2-(3,4-dimethoxyphenyl)-4,5,7,8,10,10a-hexahydropyrido[4,3-*b*]pyrrolo[3,2,1-*hi*]indole-9(6a*H*)-carboxylate;

(6a*S*,10a*R*)-2-(3,4-dimethoxyphenyl)-4,5,6a,7,8,9,10,10a-octahydropyrido [4,3-*b*]pyrrolo[3,2,1-*hi*]indole;

15 *tert*-butyl (6a*S*,10a*R*)-2-(2,5-dichlorophenyl)-4,5,7,8,10,10a-hexahydropyrido[4,3-*b*]pyrrolo[3,2,1-*hi*]indole-9(6a*H*)-carboxylate;

20 (6a*S*,10a*R*)-2-(2,5-dichlorophenyl)-4,5,6a,7,8,9,10,10a-octahydropyrido [4,3-*b*]pyrrolo[3,2,1-*hi*]indole;

tert-butyl (6a*S*,10a*R*)-2-(3,5-dichlorophenyl)-4,5,7,8,10,10a-hexahydropyrido[4,3-*b*]pyrrolo[3,2,1-*hi*]indole-9(6a*H*)-carboxylate;

25 (6a*S*,10a*R*)-2-(3,5-dichlorophenyl)-4,5,6a,7,8,9,10,10a-octahydropyrido [4,3-*b*]pyrrolo[3,2,1-*hi*]indole;

tert-butyl (6a*S*,10a*R*)-2-(2-isopropyl-4-methoxyphenyl)-4,5,7,8,10,10a-hexahydropyrido[4,3-*b*]pyrrolo[3,2,1-*hi*]indole-9(6a*H*)-carboxylate;

30 (6a*S*,10a*R*)-2-(2-isopropyl-4-methoxyphenyl)-4,5,6a,7,8,9,10,10a-octahydropyrido [4,3-*b*]pyrrolo[3,2,1-*hi*]indole;

- tert*-butyl (6a*S*,10a*R*)-2-(5-fluoro-4-methoxy-2-methylphenyl)-4,5,7,8,10,10a-hexahydropyrido[4,3-*b*]pyrrolo[3,2,1-*hi*]indole-9(6a*H*)-carboxylate;
- 5 (6a*S*,10a*R*)-2-(5-fluoro-4-methoxy-2-methylphenyl)-4,5,6a,7,8,9,10,10a-octahydropyrido [4,3-*b*]pyrrolo[3,2,1-*hi*]indole;
- tert*-butyl (6a*S*,10a*R*)-2-(4-methoxy-2-methylphenyl)-4,5,7,8,10,10a-hexahydropyrido[4,3-*b*]pyrrolo[3,2,1-*hi*]indole-9(6a*H*)-carboxylate;
- 10 (6a*S*,10a*R*)-2-(4-methoxy-2-methylphenyl)-4,5,6a,7,8,9,10,10a-octahydropyrido [4,3-*b*]pyrrolo[3,2,1-*hi*]indole;
- tert*-butyl (6a*S*,10a*R*)-2-(2-chloro-4-methoxyphenyl)-4,5,7,8,10,10a-hexahydropyrido[4,3-*b*]pyrrolo[3,2,1-*hi*]indole-9(6a*H*)-carboxylate;
- 15 (6a*S*,10a*R*)-2-(2-chloro-4-methoxyphenyl)-4,5,6a,7,8,9,10,10a-octahydropyrido [4,3-*b*]pyrrolo[3,2,1-*hi*]indole;
- tert*-butyl (6a*S*,10a*R*)-2-(3-chloro-2-methylphenyl)-4,5,7,8,10,10a-hexahydropyrido[4,3-*b*]pyrrolo[3,2,1-*hi*]indole-9(6a*H*)-carboxylate;
- 20 (6a*S*,10a*R*)-2-(3-chloro-2-methylphenyl)-4,5,6a,7,8,9,10,10a-octahydropyrido [4,3-*b*]pyrrolo[3,2,1-*hi*]indole;
- 25 2-[(6a*S*,10a*R*)-4,5,6a,7,8,9,10,10a-octahydropyrido[4,3-*b*]pyrrolo[3,2,1-*hi*]-2-yl]-5-methoxybenzaldehyde;
- (6a*S*,10a*R*)-2-(2,6-dichlorophenyl)-4,5,6a,7,8,9,10,10a-octahydropyrido[4,3-*b*]pyrrolo[3,2,1-*hi*]indole;
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- N*-[4-[(6*aS*,10*aR*)-4,5,6*a*,7,8,9,10,10*a*-octahydropyrido[4,3-*b*]pyrrolo[3,2,1-*hi*]indol-2-yl]-3-(trifluoromethyl)phenyl]-*N*-methylaniline;
- 5 4-[(6*aS*,10*aR*)-4,5,6*a*,7,8,9,10,10*a*-octahydropyrido[4,3-*b*]pyrrolo[3,2,1-*hi*]indol-2-yl]-3-(trifluoromethyl)phenylaniline;
- 1-(2-[(6*aS*,10*aR*)-4,5,6*a*,7,8,9,10,10*a*-octahydropyrido[4,3-*b*]pyrrolo[3,2,1-*hi*]indol-2-yl]-5-methoxyphenyl)ethanol;
- 10 *tert*-butyl (±)-*cis*-4,5,6,7,8*a*,9,10,11,12,12*a*-decahydroazepino[3,2,1-*hi*]pyrido[4,3-*b*]indole-11(8*aH*)-carboxylate;
- tert*-butyl (8*aS*,12*aR*)-2-bromo-4,5,6,7,8*a*,9,10,11,12,12*a*-decahydroazepino[3,2,1-*hi*]pyrido[4,3-*b*]indole-11(8*aH*)-carboxylate;
- 15 (8*aS*,12*aR*)-2-(2,4-dichlorophenyl)-4,5,6,7,8*a*,9,10,11,12,12*a*-decahydroazepino[3,2,1-*hi*]pyrido[4,3-*b*]indole;
- (8*aS*,12*aR*)-2-(2,3-dichlorophenyl)-4,5,6,7,8*a*,9,10,11,12,12*a*-decahydroazepino[3,2,1-*hi*]pyrido[4,3-*b*]indole;
- 20 (8*aS*,12*aR*)-2-(3,4-dichlorophenyl)-4,5,6,7,8*a*,9,10,11,12,12*a*-decahydroazepino[3,2,1-*hi*]pyrido[4,3-*b*]indole;
- (8*aS*,12*aR*)-2-(3,5-dichlorophenyl)-4,5,6,7,8*a*,9,10,11,12,12*a*-decahydroazepino[3,2,1-*hi*]pyrido[4,3-*b*]indole;
- 25 (8*aS*,12*aR*)-2-(2,5-dichlorophenyl)-4,5,6,7,8*a*,9,10,11,12,12*a*-decahydroazepino[3,2,1-*hi*]pyrido[4,3-*b*]indole;
- (8*aS*,12*aR*)-2-(2,6-dichlorophenyl)-4,5,6,7,8*a*,9,10,11,12,12*a*-decahydroazepino[3,2,1-*hi*]pyrido[4,3-*b*]indole;
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- (8a*S*,12a*R*)-2-(2-chlorophenyl)-4,5,6,7,8a,9,10,11,12,12a-decahydroazepino[3,2,1-*hi*]pyrido[4,3-*b*]indole;
- 5 (8a*S*,12a*R*)-2-(3-chlorophenyl)-4,5,6,7,8a,9,10,11,12,12a-decahydroazepino[3,2,1-*hi*]pyrido[4,3-*b*]indole;
- (8a*S*,12a*R*)-2-(4-chlorophenyl)-4,5,6,7,8a,9,10,11,12,12a-decahydroazepino[3,2,1-*hi*]pyrido[4,3-*b*]indole;
- 10 (±)-*cis*-2-(2,6-difluorophenyl)-4,5,6,7,8a,9,10,11,12,12a-decahydroazepino[3,2,1-*hi*]pyrido[4,3-*b*]indole;
- (8a*S*,12a*R*)-2-(2,6-difluorophenyl)-4,5,6,7,8a,9,10,11,12,12a-decahydroazepino[3,2,1-*hi*]pyrido[4,3-*b*]indole;
- 15 (8a*S*,12a*R*)-2-(2,3-difluorophenyl)-4,5,6,7,8a,9,10,11,12,12a-decahydroazepino[3,2,1-*hi*]pyrido[4,3-*b*]indole;
- (8a*S*,12a*R*)-2-(3,4-difluorophenyl)-4,5,6,7,8a,9,10,11,12,12a-decahydroazepino[3,2,1-*hi*]pyrido[4,3-*b*]indole;
- 20 (8a*S*,12a*R*)-2-(3-fluorophenyl)-4,5,6,7,8a,9,10,11,12,12a-decahydroazepino[3,2,1-*hi*]pyrido[4,3-*b*]indole;
- 25 (8a*S*,12a*R*)-2-[2-chloro-4-(trifluoromethyl)phenyl]-4,5,6,7,8a,9,10,11,12,12a-decahydroazepino[3,2,1-*hi*]pyrido[4,3-*b*]indole;
- (8a*S*,12a*R*)-2-(2-chloro-4-methoxyphenyl)-4,5,6,7,8a,9,10,11,12,12a-decahydroazepino[3,2,1-*hi*]pyrido[4,3-*b*]indole;
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(8a*S*,12a*R*)-2-(2-fluoro-4-methoxyphenyl)-4,5,6,7,8a,9,10,11,12,12a-decahydroazepino[3,2,1-*hi*]pyrido[4,3-*b*]indole;

5 (8a*S*,12a*R*)-2-(4-methoxy-2-methylphenyl)-4,5,6,7,8a,9,10,11,12,12a-decahydroazepino[3,2,1-*hi*]pyrido[4,3-*b*]indole;

(8a*S*,12a*R*)-2-[4-methoxy-2-(trifluoromethyl)phenyl]-4,5,6,7,8a,9,10,11,12,12a-decahydroazepino[3,2,1-*hi*]pyrido[4,3-*b*]indole;

10 (8a*S*,12a*R*)-2-[2-(trifluoromethyl)phenyl]-4,5,6,7,8a,9,10,11,12,12a-decahydroazepino[3,2,1-*hi*]pyrido[4,3-*b*]indole;

(8a*S*,12a*R*)-2-[4-isopropoxy-2-(trifluoromethyl)phenyl]-4,5,6,7,8a,9,10,11,12,12a-decahydroazepino[3,2,1-*hi*]pyrido[4,3-*b*]indole;

15 (8a*S*,12a*R*)-2-[2,4-bis(trifluoromethyl)phenyl]-4,5,6,7,8a,9,10,11,12,12a-decahydroazepino[3,2,1-*hi*]pyrido[4,3-*b*]indole;

20 (8a*S*,12a*R*)-2-[4-fluoro-2-(trifluoromethyl)phenyl]-4,5,6,7,8a,9,10,11,12,12a-decahydroazepino[3,2,1-*hi*]pyrido[4,3-*b*]indole;

4-[(8a*S*,12a*R*)-4,5,6,7,8a,9,10,11,12,12a-decahydroazepino[3,2,1-*hi*]pyrido[4,3-*b*]indol-2-yl]-3-(trifluoromethyl)aniline;

25 4-[(8a*S*,12a*R*)-4,5,6,7,8a,9,10,11,12,12a-decahydroazepino[3,2,1-*hi*]pyrido[4,3-*b*]indol-2-yl]-*N*-methyl-3-(trifluoromethyl)aniline;

2-[(8a*S*,12a*R*)-4,5,6,7,8a,9,10,11,12,12a-decahydroazepino[3,2,1-*hi*]pyrido[4,3-*b*]indol-2-yl]benzaldehyde;

30 {2-[(8a*S*,12a*R*)-4,5,6,7,8a,9,10,11,12,12a-decahydroazepino[3,2,1-*hi*]pyrido[4,3-*b*]indol-2-yl]phenyl}methanol;

- 2-[(8a*S*,12a*R*)-4,5,6,7,8a,9,10,11,12,12a-decahydroazepino[3,2,1-*hi*]pyrido[4,3-*b*]indol-2-yl]-5-methoxybenzaldehyde;
- 5 {2-[(8a*S*,12a*R*)-4,5,6,7,8a,9,10,11,12,12a-decahydroazepino[3,2,1-*hi*]pyrido[4,3-*b*]indol-2-yl]-5-methoxyphenyl}methanol;
- 4-[(8a*S*,12a*R*)-4,5,6,7,8a,9,10,11,12,12a-decahydroazepino[3,2,1-*hi*]pyrido[4,3-*b*]indol-2-yl]-3-methylbenzonitrile;
- 10 1-{2-[(8a*S*,12a*R*)-4,5,6,7,8a,9,10,11,12,12a-decahydroazepino[3,2,1-*hi*]pyrido[4,3-*b*]indol-2-yl]-5-methoxyphenyl}ethanol;
- 15 *tert*-butyl (7a*S*,11a*R*)-2-bromo-5,6,7a,8,9,10,11,11a-octahydro-4*H*-pyrido[3',4':4,5]pyrrolo[3,2,1-*ij*]quinoline-10(7a*H*)-carboxylate;
- (7a*S*,11a*R*)-2-(2,4-dichlorophenyl)-5,6,7a,8,9,10,11,11a-octahydro-4*H*-pyrido[3',4':4,5]pyrrolo[3,2,1-*ij*]quinoline;
- 20 (7a*S*,11a*R*)-2-(3,4-dichlorophenyl)-5,6,7a,8,9,10,11,11a-octahydro-4*H*-pyrido[3',4':4,5]pyrrolo[3,2,1-*ij*]quinoline;
- (7a*S*,11a*R*)-2-(3,5-dichlorophenyl)-5,6,7a,8,9,10,11,11a-octahydro-4*H*-pyrido[3',4':4,5]pyrrolo[3,2,1-*ij*]quinoline;
- 25 (7a*S*,11a*R*)-2-(2,5-dichlorophenyl)-5,6,7a,8,9,10,11,11a-octahydro-4*H*-pyrido[3',4':4,5]pyrrolo[3,2,1-*ij*]quinoline;
- (7a*S*,11a*R*)-2-(2,6-dichlorophenyl)-5,6,7a,8,9,10,11,11a-octahydro-4*H*-pyrido[3',4':4,5]pyrrolo[3,2,1-*ij*]quinoline;
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- (7a*S*,11a*R*)-2-(2-chlorophenyl)-5,6,7a,8,9,10,11,11a-octahydro-4*H*-pyrido[3',4':4,5]pyrrolo[3,2,1-*ij*]quinoline;
- 5 (7a*S*,11a*R*)-2-(3-chlorophenyl)-5,6,7a,8,9,10,11,11a-octahydro-4*H*-pyrido[3',4':4,5]pyrrolo[3,2,1-*ij*]quinoline;
- (7a*S*,11a*R*)-2-(4-chlorophenyl)-5,6,7a,8,9,10,11,11a-octahydro-4*H*-pyrido[3',4':4,5]pyrrolo[3,2,1-*ij*]quinoline;
- 10 (7a*S*,11a*R*)-2-(2,6-difluorophenyl)-5,6,7a,8,9,10,11,11a-octahydro-4*H*-pyrido[3',4':4,5]pyrrolo[3,2,1-*ij*]quinoline;
- (7a*S*,11a*R*)-2-(2,6-difluorophenyl)-10-methyl-5,6,7a,8,9,10,11,11a-octahydro-4*H*-pyrido[3',4':4,5]pyrrolo[3,2,1-*ij*]quinoline;
- 15 (7a*S*,11a*R*)-2-(2,3-difluorophenyl)-5,6,7a,8,9,10,11,11a-octahydro-4*H*-pyrido[3',4':4,5]pyrrolo[3,2,1-*ij*]quinoline;
- (7a*S*,11a*R*)-2-(3,4-difluorophenyl)-5,6,7a,8,9,10,11,11a-octahydro-4*H*-pyrido[3',4':4,5]pyrrolo[3,2,1-*ij*]quinoline;
- 20 (7a*S*,11a*R*)-2-(3-fluorophenyl)-5,6,7a,8,9,10,11,11a-octahydro-4*H*-pyrido[3',4':4,5]pyrrolo[3,2,1-*ij*]quinoline;
- (7a*S*,11a*R*)-2-[2-chloro-4-methoxyphenyl]-5,6,7a,8,9,10,11,11a-octahydro-4*H*-pyrido[3',4':4,5]pyrrolo[3,2,1-*ij*]quinoline;
- 25 (7a*S*,11a*R*)-2-[2-fluoro-4-methoxyphenyl]-5,6,7a,8,9,10,11,11a-octahydro-4*H*-pyrido[3',4':4,5]pyrrolo[3,2,1-*ij*]quinoline;
- 30 (7a*S*,11a*R*)-2-(4-methoxy-2-methylphenyl)-5,6,7a,8,9,10,11,11a-octahydro-4*H*-pyrido[3',4':4,5]pyrrolo[3,2,1-*ij*]quinoline;

- (7a*S*,11a*R*)-2-[4-methoxy-2-(trifluoromethyl)phenyl]-5,6,7a,8,9,10,11,11a-octahydro-4*H*-pyrido[3',4':4,5]pyrrolo[3,2,1-*ij*]quinoline;
- 5 4-[(7a*S*,11a*R*)-5,6,7a,8,9,10,11,11a-octahydro-4*H*-pyrido[3',4':4,5]pyrrolo[3,2,1-*ij*]quinolin-2-yl]-3-(trifluoromethyl)phenol;
- (7a*S*,11a*R*)-2-[2-(trifluoromethyl)phenyl]-5,6,7a,8,9,10,11,11a-octahydro-4*H*-pyrido[3',4':4,5]pyrrolo[3,2,1-*ij*]quinoline;
- 10 (7a*S*,11a*R*)-2-[4-isopropoxy-2-(trifluoromethyl)phenyl]-5,6,7a,8,9,10,11,11a-octahydro-4*H*-pyrido[3',4':4,5]pyrrolo[3,2,1-*ij*]quinoline;
- (7a*S*,11a*R*)-2-[2,4-bis(trifluoromethyl)phenyl]-5,6,7a,8,9,10,11,11a-octahydro-4*H*-pyrido[3',4':4,5]pyrrolo[3,2,1-*ij*]quinoline;
- 15 (7a*S*,11a*R*)-2-[4-fluoro-2-(trifluoromethyl)phenyl]-5,6,7a,8,9,10,11,11a-octahydro-4*H*-pyrido[3',4':4,5]pyrrolo[3,2,1-*ij*]quinoline;
- (7a*S*,11a*R*)-2-[4-fluoro-2-(trifluoromethyl)phenyl]-5,6,7a,8,9,10,11,11a-octahydro-4*H*-pyrido[3',4':4,5]pyrrolo[3,2,1-*ij*]quinoline;
- 20 4-[(7a*S*,11a*R*)-5,6,7a,8,9,10,11,11a-octahydro-4*H*-pyrido[3',4':4,5]pyrrolo[3,2,1-*ij*]quinolin-2-yl]-3-(trifluoromethyl)aniline;
- 4-[(7a*S*,11a*R*)-5,6,7a,8,9,10,11,11a-octahydro-4*H*-pyrido[3',4':4,5]pyrrolo[3,2,1-*ij*]quinolin-2-yl]-*N*-methyl-3-(trifluoromethyl)aniline;
- 25 (7a*S*,11a*R*)-5,6,7a,8,9,10,11,11a-octahydro-4*H*-pyrido[3',4':4,5]pyrrolo[3,2,1-*ij*]quinolin-2-yl]-3-methylbenzonitrile;
- 4-[(7a*S*,11a*R*)-5,6,7a,8,9,10,11,11a-octahydro-4*H*-pyrido[3',4':4,5]pyrrolo[3,2,1-*ij*]quinolin-2-yl]benzaldehyde;
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- {2-[(7a*S*,11a*R*)-5,6,7a,8,9,10,11,11a-octahydro-4*H*-pyrido[3',4':4,5]pyrrolo[3,2,1-*ij*]quinolin-2-yl]phenyl}methanol;
- 5 2-[(7a*S*,11a*R*)-5,6,7a,8,9,10,11,11a-octahydro-4*H*-pyrido[3',4':4,5]pyrrolo[3,2,1-*ij*]quinolin-2-yl]-5-methoxybenzaldehyde;
- {2-[(7a*S*,11a*R*)-5,6,7a,8,9,10,11,11a-octahydro-4*H*-pyrido[3',4':4,5]pyrrolo[3,2,1-*ij*]quinolin-2-yl]-5-methoxyphenyl}methanol;
- 10 (8a*S*,12a*R*)-2-[4-ethoxy-2-(trifluoromethyl)phenyl]-4,5,6,7,8a,9,10,11,12,12a-decahydroazepino[3,2,1-*hi*]pyrido[4,3*b*]indole;
- (7a*S*,11a*R*)-2-[4-ethoxy-2-(trifluoromethyl)phenyl]-5,6,7a,8,9,10,11,11a-octahydro-4*H*-pyrido[3',4':4,5]pyrrolo[3,2,1-*ij*]quinoline;
- 15 (8a*S*,12a*R*)-2-[3-chloro-2-methylphenyl]-4,5,6,7,8a,9,10,11,12,12a-decahydroazepino[3,2,1-*hi*]pyrido[4,3*b*]indole;
- (7a*S*,11a*R*)-2-[3-chloro-2-methylphenyl]-5,6,7a,8,9,10,11,11a-octahydro-4*H*-pyrido[3',4':4,5]pyrrolo[3,2,1-*ij*]quinoline;
- 20 (7a*S*,11a*R*)-2-[5-fluoro-2-methylphenyl]-5,6,7a,8,9,10,11,11a-octahydro-4*H*-pyrido[3',4':4,5]pyrrolo[3,2,1-*ij*]quinoline;
- (±)-*cis*-2-(2,3-dichlorophenyl)-10-propyl-5,6,7a,8,9,10,11,11a-octahydro-4*H*-pyrido[3',4':4,5]pyrrolo[3,2,1-*ij*]quinoline ;
- 25 (7a*S*,11a*R*)-2-(2,3-dichlorophenyl)-10-propyl-5,6,7a,8,9,10,11,11a-octahydro-4*H*-pyrido[3',4':4,5]pyrrolo[3,2,1-*ij*]quinoline ;
- 30 (±)-*cis*-10-butyl-2-(2,3-dichlorophenyl)-5,6,7a,8,9,10,11,11a-octahydro-4*H*-pyrido[3',4':4,5]pyrrolo[3,2,1-*ij*]quinoline ;

- (7a*S*,11a*R*)-10-butyl-2-(2,3-dichlorophenyl)-5,6,7a,8,9,10,11,11a-octahydro-4*H*-pyrido[3',4':4,5]pyrrolo[3,2,1-*ij*]quinoline ;
- 5 (7a*S*,11a*R*)-2-(2,3-dichlorophenyl)-10-(4-pentenyl)-5,6,7a,8,9,10,11,11a-octahydro-4*H*-pyrido[3',4':4,5]pyrrolo[3,2,1-*ij*]quinoline ;
- (7a*S*,11a*R*)-2-(2,3-dichlorophenyl)-10-(3-methyl-2-butenyl)-5,6,7a,8,9,10,11,11a-octahydro-4*H*-pyrido[3',4':4,5]pyrrolo[3,2,1-*ij*]quinoline;
- 10 (7a*S*,11a*R*)-2-(2,4-dichlorophenyl)-10-propyl-5,6,7a,8,9,10,11,11a-octahydro-4*H*-pyrido[3',4':4,5]pyrrolo[3,2,1-*ij*]quinoline ;
- (7a*S*,11a*R*)-10-butyl-2-(2,4-dichlorophenyl)-5,6,7a,8,9,10,11,11a-octahydro-4*H*-pyrido[3',4':4,5]pyrrolo[3,2,1-*ij*]quinoline ;
- 15 (7a*S*,11a*R*)-2-(2,4-dichlorophenyl)-10-(4-pentenyl)-5,6,7a,8,9,10,11,11a-octahydro-4*H*-pyrido[3',4':4,5]pyrrolo[3,2,1-*ij*]quinoline ;
- (7a*S*,11a*R*)-2-(2,4-dichlorophenyl)-10-(3-methyl-2-butenyl)-5,6,7a,8,9,10,11,11a-octahydro-4*H*-pyrido[3',4':4,5]pyrrolo[3,2,1-*ij*]quinoline;
- 20 (7a*S*,11a*R*)-10-(cyclobutylmethyl)-2-(2,3-dichlorophenyl)-5,6,7a,8,9,10,11,11a-octahydro-4*H*-pyrido[3',4':4,5]pyrrolo[3,2,1-*ij*]quinoline;
- 25 (7a*S*,11a*R*)-2-[4-methoxy-2-(trifluoromethyl)phenyl]-10-methyl-5,6,7a,8,9,10,11,11a-octahydro-4*H*-pyrido[3',4':4,5]pyrrolo[3,2,1-*ij*]quinoline;
- (7a*S*,11a*R*)-10-ethyl-2-[4-methoxy-2-(trifluoromethyl)phenyl]-5,6,7a,8,9,10,11,11a-octahydro-4*H*-pyrido[3',4':4,5]pyrrolo[3,2,1-*ij*]quinoline;
- 30

- (7a*S*,11a*R*)-2-[4-methoxy-2-(trifluoromethyl)phenyl]-10-propyl-
5,6,7a,8,9,10,11,11a-octahydro-4*H*-pyrido[3',4':4,5]pyrrolo[3,2,1-*ij*]quinoline;
- (7a*S*,11a*R*)-10-butyl-2-[4-methoxy-2-(trifluoromethyl)phenyl]-10-methyl-
5 5,6,7a,8,9,10,11,11a-octahydro-4*H*-pyrido[3',4':4,5]pyrrolo[3,2,1-*ij*]quinoline;
- (7a*S*,11a*R*)-2-[4-methoxy-2-(trifluoromethyl)phenyl]-10-(4-pentenyl)-
5,6,7a,8,9,10,11,11a-octahydro-4*H*-pyrido[3',4':4,5]pyrrolo[3,2,1-*ij*]quinoline;
- 10 (7a*S*,11a*R*)-2-[4-methoxy-2-(trifluoromethyl)phenyl]-10-(3-methyl-2-butenyl)-
5,6,7a,8,9,10,11,11a-octahydro-4*H*-pyrido[3',4':4,5]pyrrolo[3,2,1-*ij*]quinoline;
- (7a*S*,11a*R*)-10-(2-fluoroethyl)-2-[4-methoxy-2-(trifluoromethyl)phenyl]-
5,6,7a,8,9,10,11,11a-octahydro-4*H*-pyrido[3',4':4,5]pyrrolo[3,2,1-*ij*]quinoline;
- 15 (7a*S*,11a*R*)-10-(2,2-difluoroethyl)-2-[4-methoxy-2-(trifluoromethyl)phenyl]-
5,6,7a,8,9,10,11,11a-octahydro-4*H*-pyrido[3',4':4,5]pyrrolo[3,2,1-*ij*]quinoline;
- (7a*S*,11a*R*)-10-(cyclobutylmethyl)-2-[4-methoxy-2-(trifluoromethyl)phenyl]-
20 5,6,7a,8,9,10,11,11a-octahydro-4*H*-pyrido[3',4':4,5]pyrrolo[3,2,1-*ij*]quinoline;
- 4-((7a*S*,11a*R*)-5,6,8,9,11,11a-hexahydro-4*H*-pyrido[3',4':4,5]pyrrolo[3,2,1-
ij]quinolin-10(7a*H*)-yl)-1-(4-fluorophenyl)-1-butanone;
- 25 4-((7a*R*,11a*S*)-5,6,8,9,11,11a-hexahydro-4*H*-pyrido[3',4':4,5]pyrrolo[3,2,1-
ij]quinolin-10(7a*H*)-yl)-1-(4-fluorophenyl)-1-butanone;
- 4-((7a*S*,11a*R*)-5,6,8,9,11,11a-hexahydro-4*H*-pyrido[3',4':4,5]pyrrolo[3,2,1-
ij]quinolin-10(7a*H*)-yl)-1-(2-aminophenyl)-1-butanone;
- 30 4-((7a*R*,11a*S*)-5,6,8,9,11,11a-hexahydro-4*H*-pyrido[3',4':4,5]pyrrolo[3,2,1-
ij]quinolin-10(7a*H*)-yl)-1-(2-aminophenyl)-1-butanone;

- (±)-*cis*-3-(5,6,8,9,11,11a-hexahydro-4*H*-pyrido[3',4':4,5]pyrrolo[3,2,1-*ij*]quinolin-10(7*aH*)-yl)propyl 4-fluorophenyl ether;
- 5 4-((±)-*cis*-5,6,8,9,11,11a-hexahydro-4*H*-pyrido[3',4':4,5]pyrrolo[3,2,1-*ij*]quinolin-10(7*aH*)-yl)-1-(4-pyridinyl)-1-butanone;
- (±)-*cis*-10-[3-(6-fluoro-1,2-benzisoxazol-3-yl)propyl]-5,6,7*a*,8,9,10,11,11*a*-octahydro-4*H*-pyrido[3',4':4,5]pyrrolo[3,2,1-*ij*]quinoline;
- 10 (7*aS*,11*aR*)-10-[3-(6-fluoro-1,2-benzisoxazol-3-yl)propyl]-5,6,7*a*,8,9,10,11,11*a*-octahydro-4*H*-pyrido[3',4':4,5]pyrrolo[3,2,1-*ij*]quinoline;
- (±)-*cis*-4-(4,5,6,7,9,10,12,12*a*-octahydroazepino[3,2,1-*hi*]pyrido[4,3-*b*]indol-11(8*aH*)-yl)-1-(4-fluorophenyl)-1-butanone;
- 15 4-((8*aS*,12*aR*)-4,5,6,7,9,10,12,12*a*-octahydroazepino[3,2,1-*hi*]pyrido[4,3-*b*]indol-11(8*aH*)-yl)-1-(4-fluorophenyl)-1-butanone;
- 4-((8*aR*,12*aS*)-4,5,6,7,9,10,12,12*a*-octahydroazepino[3,2,1-*hi*]pyrido[4,3-*b*]indol-11(8*aH*)-yl)-1-(4-fluorophenyl)-1-butanone;
- 20 4-((±)-4,5,6,7,9,10,12,12*a*-octahydroazepino[3,2,1-*hi*]pyrido[4,3-*b*]indol-11(8*aH*)-yl)-1-(2-amino-4-fluorophenyl)-1-butanone;
- 25 4-((±)-*cis*-5,6,8,9,11,11a-hexahydro-4*H*-pyrido[3',4':4,5]pyrrolo[3,2,1-*ij*]quinolin-10(7*aH*)-yl)-1-(2-amino-4-fluorophenyl)-1-butanone ;
- 4-((7*aS*,11*aR*)-5,6,8,9,11,11a-hexahydro-4*H*-pyrido[3',4':4,5]pyrrolo[3,2,1-*ij*]quinolin-10(7*aH*)-yl)-1-(2-amino-4-fluorophenyl)-1-butanone; and
- 30

4-((7a*R*,11a*S*)-5,6,8,9,11,11a-hexahydro-4*H*-pyrido[3',4':4,5]pyrrolo[3,2,1-*ij*]quinolin-10(7a*H*)-yl)-1-(2-amino-4-fluorophenyl)-1-butanone.

5 In a more preferred embodiment, the present invention provides the method as defined in Claim 18 where the compound administered is selected from the group:

4-[(±)-5,6,8,9,10,11,12,12a-octahydro-4*H*,7a*H*-azepino[4',5':4,5]pyrrolo
[3,2,1-*ij*]quinolin-10-yl]-1-(4-fluorophenyl)-1-butanone;

10

4-[(±)-5,6,8,9,10,11,12,12a-octahydro-4*H*,7a*H*-azepino[4',5':4,5]pyrrolo
[3,2,1-*ij*]quinolin-10-yl]-1-(2-amino-4-fluorophenyl)-1-butanone;

4-[(±)-4,5,6,7,9,10,11,12,13,13a-decahydro-11*H*-diazepino[4,5-*b*:3,2,1-*hi*]
indol-11-yl]-1-(4-fluorophenyl)-1-butanone;

15

4-[(±)-4,5,6,7,9,10,11,12,13,13a-decahydro-11*H*-diazepino[4,5-*b*:3,2,1-*hi*]
indol-11-yl]-1-(2-amino-4-fluorophenyl)-1-butanone;

20 *tert*-butyl (±)-*cis*-5,6,8,9,10,11,12,12a-octahydro-4*H*,7a*H*-
azepino[3',4':4,5]pyrrolo[3,2,1-*ij*]quinoline-11-carboxylate;

tert-butyl (±)-*cis*-2-bromo-5,6,8,9,10,11,12,12a-octahydro-4*H*,7a*H*-
azepino[3',4':4,5]pyrrolo[3,2,1-*ij*]quinoline-11-carboxylate; and

25

(±)-*cis*-2-[4-methoxy-2-(trifluoromethyl)phenyl]-5,6,8,9,10,11,12,12a-
octahydro-4*H*,7a*H*-azepino[3',4':4,5]pyrrolo[3,2,1-*ij*]quinoline.

30 In a more preferred embodiment, the present invention provides the method as defined in Claim 18 where the compound administered is selected from the group:

tert-butyl (±)-*cis*-2-bromo-4-oxo-4,5,6,7,9,10,12,12a-octahydroazepino[3,2,1-*hi*]pyrido[4,3-*b*]indole-11(8a*H*)-carboxylate;

5 *tert*-butyl (±)-*cis*-2-(2,4-dichlorophenyl)-4-oxo-4,5,6,7,9,10,12,12a-octahydroazepino[3,2,1-*hi*]pyrido[4,3-*b*]indole-11(8a*H*)-carboxylate;

(±)-*cis*-2-(2,4-dichlorophenyl)-6,7,8a,9,10,11,12,12a-octahydroazepino[3,2,1-*hi*]pyrido[4,3-*b*]indol-4(5*H*)-one;

10

(8a*S*, 12a*R*)-2-(2,4-dichlorophenyl)-6,7,8a,9,10,11,12,12a-octahydroazepino[3,2,1-*hi*]pyrido[4,3-*b*]indol-4(5*H*)-one;

15

(8a*R*, 12a*S*)-2-(2,4-dichlorophenyl)-6,7,8a,9,10,11,12,12a-octahydroazepino[3,2,1-*hi*]pyrido[4,3-*b*]indol-4(5*H*)-one;

(8a*S*, 12a*R*)-2-(2,4-dichlorophenyl)-6,7,8a,9,10,11,12,12a-decahydroazepino[3,2,1-*hi*]pyrido[4,3-*b*]indol-4-ol; and

20

(8a*R*, 12a*S*)-2-(2,4-dichlorophenyl)-6,7,8a,9,10,11,12,12a-decahydroazepino[3,2,1-*hi*]pyrido[4,3-*b*]indol-4-ol.

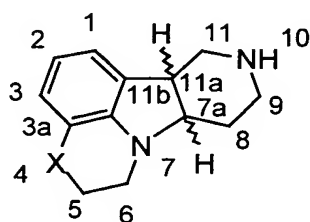
DEFINITIONS

25 As used herein, the term "addictive behavior" includes behaviors associated with and/or caused by physical and/or psychological dependence on narcotics, opiates, analgesics, painkillers, amphetamines, cocaine, heroin, opium, marijuana, alcohol, smoking, nicotine, gambling and eating.

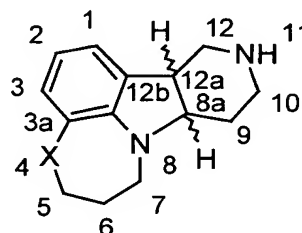
30 The term "sleep disorders," as used herein, includes insomnia, narcolepsy and sleep apnea.

The compounds herein described may have asymmetric centers. Compounds of the present invention containing an asymmetrically substituted atom may be isolated in optically active or racemic forms. It is well known in the art how to prepare optically active forms, such as by resolution of racemic forms or by synthesis from optically active starting materials. Many geometric isomers of olefins, C=N double bonds, and the like can also be present in the compounds described herein, and all such stable isomers are contemplated in the present invention. Cis and trans geometric isomers of the compounds of the present invention are described and may be isolated as a mixture of isomers or as separated isomeric forms. All chiral, diastereomeric, racemic forms and all geometric isomeric forms of a structure are intended, unless the specific stereochemistry or isomeric form is specifically indicated.

The numbering of the tetracyclic ring-system present in the compounds of Formula (I), as defined by nomenclature known to one skilled in the art, is shown for two examples in Formula (I'), when k is 1, m is 1, and n is 1; and in Formula (I''), when k is 1, m is 1, and n is 2:



(I')



(I'')

20

The tetracyclic ring-system present in compounds of Formula (I) occur as “cis” or “trans” isomers when the carbon-carbon bond b in Formula (I) is a single bond. As such, the terms “cis” and “trans”, in conjunction with the tetracyclic ring structure, refer to the configuration of hydrogen atoms on carbon atoms 7a and 11a in Formula (I') or, for example, on carbon atoms 8a and 12a in Formula (I''), above. When both hydrogens are on the same side of the mean plane determined by the octahydro tetracyclic moiety then the configuration is designated “cis”, if not, the configuration

25

is designated "trans". It is understood that the above example is for demonstrative purposes only and not intended to limit the scope of the tetracyclic ring-system present in compounds of Formula (I). As such, it is understood that one skilled in the art of organic chemistry can apply the above numbering system to other values of k, m, and n in the scope of compounds of Formula (I) to determine the appropriate numbering. Additional Examples of the numbering of the tetracyclic ring-system are further provided below in the synthetic Examples. Lastly, it is understood that the use of "cis" or "trans" in the identification of the tetracyclic ring-system is not meant to construe the configuration of any other cis or trans geometric isomer in the molecule, for example, cis or trans butene.

The term "substituted," as used herein, means that any one or more hydrogens on the designated atom is replaced with a selection from the indicated group, provided that the designated atom's normal valency is not exceeded, and that the substitution results in a stable compound. When a substituent is keto (i.e., =O), then 2 hydrogens on the atom are replaced.

When any variable (e.g., R^2) occurs more than one time in any constituent or formula for a compound, its definition at each occurrence is independent of its definition at every other occurrence. Thus, for example, if a group is shown to be substituted with 0-2 R^2 , then said group may optionally be substituted with up to two R^2 groups and R^2 at each occurrence is selected independently from the definition of R^2 . Also, combinations of substituents and/or variables are permissible only if such combinations result in stable compounds.

When a bond to a substituent is shown to cross a bond connecting two atoms in a ring, then such substituent may be bonded to any atom on the ring. When a substituent is listed without indicating the atom via which such substituent is bonded to the rest of the compound of a given formula, then such substituent may be bonded via any atom in such substituent. Combinations of substituents and/or variables are permissible only if such combinations result in stable compounds.

As used herein, "alkyl" or "alkylene" is intended to include both branched and straight-chain saturated aliphatic hydrocarbon groups having the specified number of carbon atoms; for example, "C₁-C₆ alkyl" denotes alkyl having 1 to 6 carbon atoms.

Examples of alkyl include, but are not limited to, methyl, ethyl, n-propyl, i-propyl, n-butyl, i-butyl, sec-butyl, t-butyl, n-pentyl, n-hexyl, 2-methylbutyl, 2-methylpentyl, 2-ethylbutyl, 3-methylpentyl, and 4-methylpentyl.

"Alkenyl" or "alkenylene" is intended to include hydrocarbon chains of either
 5 a straight or branched configuration having the specified number of carbon atoms and one or more unsaturated carbon-carbon bonds which may occur in any stable point along the chain. Examples of alkenyl include, but are not limited to, ethenyl, 1-propenyl, 2-propenyl, 2-butenyl, 3-butenyl, 2-pentenyl, 3-pentenyl, 4-pentenyl, 2-hexenyl, 3-hexenyl, 4-hexenyl, 5-hexenyl, 2-methyl-2-propenyl, 4-methyl-3-pentenyl,
 10 and the like.

"Alkynyl" or "alkynylene" is intended to include hydrocarbon chains of either a straight or branched configuration and one or more carbon-carbon triple bonds which may occur in any stable point along the chain, such as ethynyl, propynyl, butynyl, pentynyl, hexynyl and the like.

15 "Cycloalkyl" is intended to include saturated ring groups, having the specified number of carbon atoms. For example, "C₃-C₆ cycloalkyl" denotes such as cyclopropyl, cyclobutyl, cyclopentyl, or cyclohexyl.

"Alkoxy" or "alkyloxy" represents an alkyl group as defined above with the indicated number of carbon atoms attached through an oxygen bridge. Examples of
 20 alkoxy include, but are not limited to, methoxy, ethoxy, n-propoxy, i-propoxy, n-butoxy, s-butoxy, t-butoxy, n-pentoxy, and s-pentoxy. Similarly, "alkylthio" is represents an alkyl group as defined above with the indicated number of carbon atoms attached through a sulphur bridge.

"Halo" or "halogen" as used herein refers to fluoro, chloro, bromo, and iodo;
 25 and "counterion" is used to represent a small, negatively charged species such as chloride, bromide, hydroxide, acetate, sulfate, and the like.

"Haloalkyl" is intended to include both branched and straight-chain saturated aliphatic hydrocarbon groups having the specified number of carbon atoms, substituted with 1 or more halogen (for example -C_vF_w where v = 1 to 3 and w = 1 to
 30 (2v+1)). Examples of haloalkyl include, but are not limited to, trifluoromethyl,

trichloromethyl, pentafluoroethyl, pentachloroethyl, 2,2,2-trifluoroethyl, heptafluoropropyl, and heptachloropropyl.

As used herein, "carbocycle" is intended to mean any stable 3- to 7-membered monocyclic or bicyclic or 7- to 13-membered bicyclic or tricyclic, any of which may be saturated, partially unsaturated, or aromatic. Examples of such carbocycles include, but are not limited to, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, adamantyl, cyclooctyl, [3.3.0]bicyclooctane, [4.3.0]bicyclononane, [4.4.0]bicyclodecane (decalin), [2.2.2]bicyclooctane, fluorenyl, phenyl, naphthyl, indanyl, adamantyl, or tetrahydronaphthyl (tetralin).

As used herein, the term "heterocycle" or "heterocyclic ring" is intended to mean a stable 5- to 7- membered monocyclic or bicyclic or 7- to 14-membered bicyclic heterocyclic ring which is saturated partially unsaturated or unsaturated (aromatic), and which consists of carbon atoms and 1, 2, 3 or 4 heteroatoms independently selected from the group consisting of N, O and S and including any bicyclic group in which any of the above-defined heterocyclic rings is fused to a benzene ring. The nitrogen and sulfur heteroatoms may optionally be oxidized. The heterocyclic ring may be attached to its pendant group at any heteroatom or carbon atom which results in a stable structure. The heterocyclic rings described herein may be substituted on carbon or on a nitrogen atom if the resulting compound is stable. If specifically noted, a nitrogen in the heterocycle may optionally be quaternized. It is preferred that when the total number of S and O atoms in the heterocycle exceeds 1, then these heteroatoms are not adjacent to one another. It is preferred that the total number of S and O atoms in the heterocycle is not more than 1.

Examples of heterocycles include, but are not limited to, 1H-indazole, 2-pyrrolidonyl, 2H,6H-1,5,2-dithiazinyl, 2H-pyrrolyl, 3H-indolyl, 4-piperidonyl, 4aH-carbazole, 4H-quinoliziny, 6H-1,2,5-thiadiazinyl, acridinyl, azocinyl, benzimidazolyl, benzofuranyl, benzothiofuranyl, benzothiophenyl, benzoxazolyl, benzoxazoliny, benzthiazolyl, benztriazolyl, benztetrazolyl, benzisoxazolyl, benzisothiazolyl, benzimidazalonyl, carbazolyl, 4aH-carbazolyl, b-carboliny, chromanyl, chromenyl, cinnoliny, decahydroquinoliny, 2H,6H-1,5,2-dithiazinyl, dihydrofuro[2,3-b]tetrahydrofuran, furanyl, furazanyl, imidazolidiny, imidazoliny, imidazolyl, imidazolopyridiny, 1H-indazolyl, indolenyl, indoliny, indoliziny, indolyl, isatinoyl,

isobenzofuranyl, isochromanyl, isoindazolyl, isoindolinyl, isoindolyl, isoquinolinyl, isothiazolyl, isothiazolopyridinyl, isoxazolyl, isoxazolopyridinyl, morpholinyl, naphthyridinyl, octahydroisoquinolinyl, oxadiazolyl, 1,2,3-oxadiazolyl, 1,2,4-oxadiazolyl, 1,2,5-oxadiazolyl, 1,3,4-oxadiazolyl, oxazolidinyl, oxazolyl, 5 oxazolopyridinyl, oxazolidinylperimidinyl, oxindolyl, phenanthridinyl, phenanthrolinyl, phenarsazinyl, phenazinyl, phenothiazinyl, phenoxathiinyl, phenoxazinyl, phthalazinyl, piperazinyl, piperidinyl, pteridinyl, piperidonyl, 4-piperidonyl, pteridinyl, purinyl, pyranyl, pyrazinyl, pyrazolidinyl, pyrazolinyl, pyrazolopyridinyl, pyrazolyl, pyridazinyl, pyridooxazole, pyridoimidazole, 10 pyridothiazole, pyridinyl, pyridyl, pyrimidinyl, pyrrolidinyl, pyrrolinyl, pyrrolyl, quinazolinyl, quinolinyl, 4*H*-quinolizinyl, quinoxalinyl, quinuclidinyl, carbolinyl, tetrahydrofuranyl, tetrahydroisoquinolinyl, tetrahydroquinolinyl, 6*H*-1,2,5-thiadiazinyl, 1,2,3-thiadiazolyl, 1,2,4-thiadiazolyl, 1,2,5-thiadiazolyl, 1,3,4-thiadiazolyl, thianthrenyl, thiazolyl, thiazolopyridinyl, thienyl, thienothiazolyl, 15 thienooxazolyl, thienoimidazolyl, thiophenyl, triazinyl, 1,2,3-triazolyl, 1,2,4-triazolyl, 1,2,5-triazolyl, 1,3,4-triazolyl, and xanthenyl. Preferred heterocycles include, but are not limited to, pyridinyl, furanyl, thienyl, pyrrolyl, pyrazolyl, pyrazinyl, piperazinyl, imidazolyl, indolyl, benzimidazolyl, 1*H*-indazolyl, oxazolidinyl, benzotriazolyl, benzisoxazolyl, benzoxazolyl, oxindolyl, benzoxazolyl, benzthiazolyl, 20 benzisothiazolyl, isatinoyl, isoxazolopyridinyl, isothiazolopyridinyl, thiazolopyridinyl, oxazolopyridinyl, imidazolopyridinyl, and pyrazolopyridinyl. Preferred 5 to 6 membered heterocycles include, but are not limited to, pyridinyl, furanyl, thienyl, pyrrolyl, pyrazolyl, pyrazinyl, piperazinyl, imidazolyl, and oxazolidinyl. Also included are fused ring and spiro compounds containing, for example, the above 25 heterocycles.

As used herein, the term "bicyclic heterocyclic ring system" is intended to mean a stable 9- to 10-membered bicyclic heterocyclic ring formed from the substituent NR¹²R¹³, which is partially unsaturated or unsaturated (aromatic), and which consists of carbon atoms, a nitrogen atom, and 1 or 2 additional heteroatoms 30 independently selected from the group consisting of N, O and S. The additional nitrogen or sulfur heteroatoms may optionally be oxidized. The heterocyclic ring is attached to its pendant group by the nitrogen atom of the group NR¹²R¹³ and for

which results in a stable structure. The heterocyclic rings described herein may be substituted on carbon or on a nitrogen atom if the resulting compound is stable. If specifically noted, a nitrogen in the heterocycle may optionally be quaternized. It is preferred that when the total number of S and O atoms in the heterocycle exceeds 1,
5 then these heteroatoms are not adjacent to one another. It is preferred that the total number of S and O atoms in the heterocycle is not more than 1. The term "bicyclic heterocyclic ring system" is intended to be a subset of the term "heterocyclic ring system". Preferred examples of a 9- to 10- membered bicyclic heterocyclic ring system are benzimidazolyl, benzimidazolyl, benzoxazolyl, dihydrobenzthiazolyl,
10 dihydrodioxobenzthiazolyl, benzisoxazolyl, 1*H*-indazolyl, indolyl, indolyl, isoindolyl, tetrahydro-isoquinolyl, tetrahydro-quinolyl, and benzotriazolyl.

Additionally, a subclass of preferred heterocycles are heterocycles which function as an isostere of a cyclic but non-heterocyclic substituent such as -CH₂-C(=O)-phenyl. Preferred examples of such heterocycles include, but are not limited
15 to, benzimidazolyl, benzofuranyl, benzothiophenyl, benzoxazolyl, benzthiazolyl, benzisoxazolyl, furanyl, imidazolyl, 1*H*-indazolyl, indolyl, isoindolyl, isoquinolyl, oxazolyl, piperidyl, pyrazinyl, pyridyl, pyrimidinyl, quinolyl, thiazolyl, thiophenyl, and 1,2,3-triazolyl.

As used herein, the term "aryl", or aromatic residue, is intended to mean an
20 aromatic moiety containing the specified number of carbon atoms, such as phenyl, pyridyl and naphthyl.

The phrase "pharmaceutically acceptable" is employed herein to refer to those compounds, materials, compositions, and/or dosage forms which are, within the scope of sound medical judgment, suitable for use in contact with the tissues of human
25 beings and animals without excessive toxicity, irritation, allergic response, or other problem or complication, commensurate with a reasonable benefit/risk ratio.

As used herein, "pharmaceutically acceptable salts" refer to derivatives of the disclosed compounds wherein the parent compound is modified by making acid or base salts thereof. Examples of pharmaceutically acceptable salts include, but are not
30 limited to, mineral or organic acid salts of basic residues such as amines; alkali or organic salts of acidic residues such as carboxylic acids; and the like. The pharmaceutically acceptable salts include the conventional non-toxic salts or the

quaternary ammonium salts of the parent compound formed, for example, from non-toxic inorganic or organic acids. For example, such conventional non-toxic salts include those derived from inorganic acids such as hydrochloric, hydrobromic, sulfuric, sulfamic, phosphoric, nitric and the like; and the salts prepared from organic acids such as acetic, propionic, succinic, glycolic, stearic, lactic, malic, tartaric, citric, ascorbic, pantoic, maleic, hydroxymaleic, phenylacetic, glutamic, benzoic, salicylic, sulfanilic, 2-acetoxybenzoic, fumaric, toluenesulfonic, methanesulfonic, ethane disulfonic, oxalic, isethionic, and the like.

The pharmaceutically acceptable salts of the present invention can be synthesized from the parent compound which contains a basic or acidic moiety by conventional chemical methods. Generally, such salts can be prepared by reacting the free acid or base forms of these compounds with a stoichiometric amount of the appropriate base or acid in water or in an organic solvent, or in a mixture of the two; generally, nonaqueous media like ether, ethyl acetate, ethanol, isopropanol, or acetonitrile are preferred. Lists of suitable salts are found in *Remington's Pharmaceutical Sciences*, 17th ed., Mack Publishing Company, Easton, PA, 1985, p. 1418, the disclosure of which is hereby incorporated by reference.

"Prodrugs" are intended to include any covalently bonded carriers which release the active parent drug according to formula (I) *in vivo* when such prodrug is administered to a mammalian subject. Prodrugs of a compound of formula (I) are prepared by modifying functional groups present in the compound in such a way that the modifications are cleaved, either in routine manipulation or *in vivo*, to the parent compound. Prodrugs include compounds of formula (I) wherein a hydroxy, amino, or sulfhydryl group is bonded to any group that, when the prodrug or compound of formula (I) is administered to a mammalian subject, cleaves to form a free hydroxyl, free amino, or free sulfhydryl group, respectively. Examples of prodrugs include, but are not limited to, acetate, formate and benzoate derivatives of alcohol and amine functional groups in the compounds of Formula (I), and the like.

"Stable compound" and "stable structure" are meant to indicate a compound that is sufficiently robust to survive isolation to a useful degree of purity from a reaction mixture, and formulation into an efficacious therapeutic agent.

SYNTHESIS

Throughout the details of the invention, the following abbreviations are used with the following meanings:

5 **Reagents:**

MCPBA m-chloroperoxybenzoic acid

DIBAL diisobutyl aluminum hydride

Et₃N triethylamine

TFA trifluoroacetic acid

10 LAH lithium aluminum hydride

NBS N-bromo succinimide

Red-Al Sodium bis(2-methoxyethoxy)aluminum hydride

Pd₂dba₃ Tris(dibenzylideneacetone)dipalladium(0)

ACE-Cl 2-chloroethylchloroformate

15

Solvents:

THF tetrahydrofuran

MeOH methanol

EtOH ethanol

20 EtOAc ethyl acetate

HOAc acetic acid

DMF dimethyl formamide

DMSO dimethyl sulfoxide

DME dimethoxyethane

25 Et₂O diethylether

iPrOH isopropanol

MEK methyl ethyl ketone

Others:

30 Ar aryl

Ph phenyl

Me methyl

	Et	ethyl
	NMR	nuclear magnetic resonance
	MHz	megahertz
	BOC	tert-butoxycarbonyl
5	CBZ	benzyloxycarbonyl
	Bn	benzyl
	Bu	butyl
	Pr	propyl
	cat.	catalytic
10	mL	milliliter
	nM	nanometer
	ppm	part per million
	mmol	millimole
	mg	milligram
15	g	gram
	kg	kilogram
	TLC	thin layer chromatography
	HPLC	high pressure liquid chromatography
	RPM	revolutions per minute
20	rt	room temperature
	aq.	aqueous
	sat.	saturated

The compounds of the present invention can be prepared in a number of ways well known to one skilled in the art of organic synthesis. The compounds of the present invention can be synthesized using the methods described below, together with synthetic methods known in the art of synthetic organic chemistry, or variations thereon as appreciated by those skilled in the art. Preferred methods include, but are not limited to, those described below. All references cited herein are hereby incorporated in their entirety herein by reference.

The novel compounds of this invention may be prepared using the reactions and techniques described in this section. The reactions are performed in solvents

appropriate to the reagents and materials employed and are suitable for the transformations being effected. Also, in the description of the synthetic methods described below, it is to be understood that all proposed reaction conditions, including choice of solvent, reaction atmosphere, reaction temperature, duration of the
5 experiment and workup procedures, are chosen to be the conditions standard for that reaction, which should be readily recognized by one skilled in the art. It is understood by one skilled in the art of organic synthesis that the functionality present on various portions of the molecule must be compatible with the reagents and reactions proposed. Such restrictions to the substituents which are compatible with the reaction
10 conditions will be readily apparent to one skilled in the art and alternate methods must then be used.

The preparation of compounds of Formula (I) of the present invention may be carried out in a convergent or sequential synthetic manner. Detailed synthetic preparations of the compounds of Formula (I) are shown in the following reaction
15 schemes. The skills required in preparation and purification of the compounds of Formula (I) and the intermediates leading to these compounds are known to those in the art. Purification procedures include, but are not limited to, normal or reverse phase chromatography, crystallization, and distillation.

Several methods for the preparation of the compounds of the present invention
20 are illustrated in the schemes and examples shown below. The substitutions are as described and defined above.

Compounds of Formula (I) of this invention may be prepared as shown in Scheme 1. Thus, preparation of an aryl hydrazine (III) is accomplished, for example, by treatment of a corresponding substituted aniline (II) with NaNO_2 followed by
25 reduction of the N-nitroso intermediate with a reducing agent such as LAH or zinc and an organic acid, such as acetic acid or trifluoroacetic acid at low temperature. Assembly of the core tetracyclic intermediate indole (V) is accomplished by Fischer indole cyclization of the aryl hydrazine and a suitably substituted ketone (i.e. (IV)) by methods described by, but not limited to, R.J. Sundberg, "Indoles, Best Synthetic
30 Methods" 1996, Academic Press, San Diego, CA. For example, treatment of the aryl hydrazine (III) as the free base or the corresponding mineral acid salt with the ketone

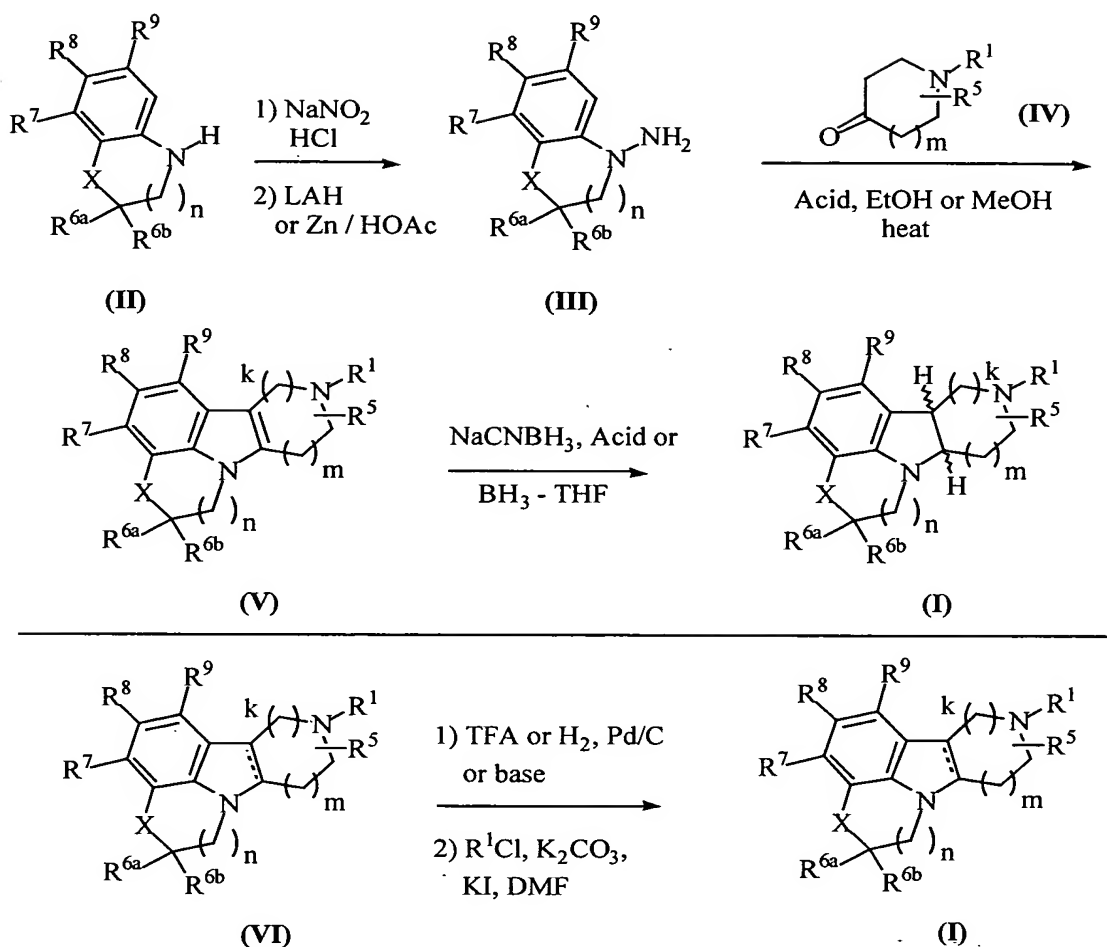
(IV) ($R^1 = H, Bn, CBZ, CO_2Et$, etc) in an alcoholic solvent in the presence of mineral acid affords the indoles (V) as the free bases (after treatment with aq. NaOH).

Reduction of the indoles to the corresponding cis or trans substituted dihydroindoles is accomplished by, for example, treatment with hydrogen in the presence of a catalyst
5 such as platinum oxide or palladium on carbon, or with a metal such as zinc and a mineral acid such as hydrochloric acid, or with sodium and liquid ammonia, or with borane-amine complex such as borane-triethylamine in tetrahydrofuran, or preferably by treatment with $NaCNBH_3$ in an acid such as acetic or trifluoroacetic acid.

The corresponding enantiomers can be isolated by separation of the racemic
10 mixture of (I) on a chiral stationary phase column utilizing normal or reverse phase HPLC techniques, the details of which are described in the examples. Alternatively, a diastereomeric mixture of (I) can be prepared by treatment of (I, $R^1 = H$) with an appropriate chiral acid (or suitably activated derivative), for example dibenzoyl tartrate or the like (see, for example, Kinbara, K., et. al., *J. Chem. Soc., Perkin Trans.*
15 *2*, **1996**, 2615; and Tomori, H., et. al., *Bull. Chem. Soc. Jpn.*, **1996**, 3581). The diastereomers would then be separated by traditional techniques (i.e. silica chromatography, crystallization, HPLC, etc) followed by removal of the chiral auxiliary to afford enantiomerically pure (I).

In the cases where the carboline nitrogen has been protected (VI) (i.e. $R^1 =$
20 Boc, Bn, CBZ, CO_2R), it may be removed under a variety of conditions as described in Greene, T.W., Wuts, P.G.W., "Protective Groups in Organic Synthesis, 2nd Edition", John Wiley and Sons, Inc., New York, pages 309-405, **1991**. The free secondary amine could then be alkylated, for example, by treatment with a suitably substituted alkyl halide (R^1Cl , or R^1I) and a base to afford additional compounds of
25 type (I), as described, for example, by Glennon, R.A., et. al., *Med. Chem. Res.*, **1996**, 197.

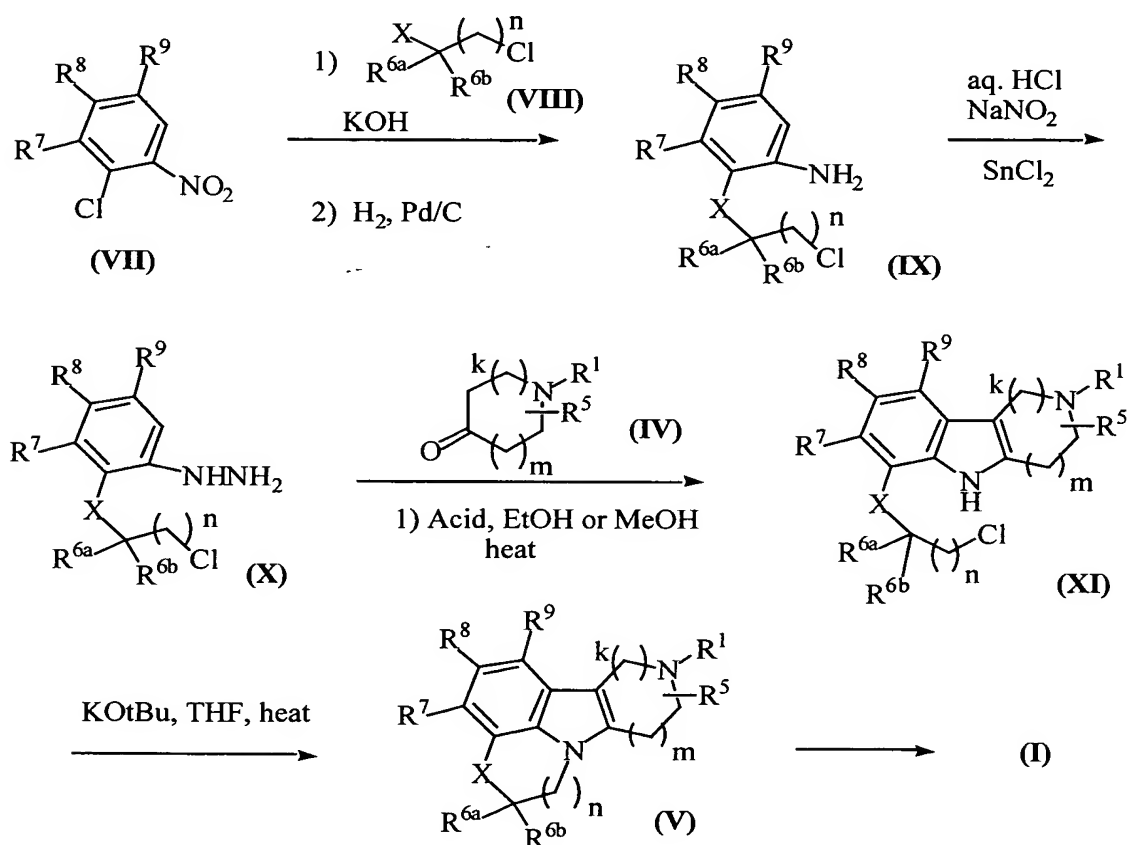
SCHEME 1



Alternatively, compounds of Formula (I) can be prepared as described in Scheme 2. Treatment of an ortho halonitrobenzene compound (VII) with a nucleophilic alkyl halide (X = OH, SH, NHR, (VIII)) (as described by Kharasch, N., Langford, R.B., *J. Org. Chem.*, **1963**, 1903) and a suitable base followed by subsequent reduction of the corresponding nitroaryl derivative to the aniline (IX). The reduction may be accomplished with a variety of reducing agents, for example, LAH, SnCl₂, NaBH₄, N₂H₄, etc. or with hydrogen in the presence of a suitable catalyst, such as palladium on carbon, or platinum oxide, etc., (see Hudlicky, M., "Reductions in Organic Chemistry", Ellis Horwood, Ltd., Chichester, UK, **1984**). Formation of the aryl hydrazine (X) may be accomplished as described previously in Scheme 1 or more directly by treatment of the aniline (IX) with aq. hydrochloric acid,

stannous chloride and NaNO_2 at room temperature (see, Buck, J.S., Ide, W.S., *Org. Syn., Coll. Vol.*, 2, 1943, 130). This primary aryl hydrazine (X) can then be cyclized under Fischer indole cyclization conditions as detailed above for compound (V), to afford the indole (XI) as the corresponding salt. Upon treatment of the indole (XI) with a base such potassium hydroxide or potassium t-butoxide in a solvent such as DME or THF affords the tetracyclic indole intermediates (V). These indoles can also be reduced to the corresponding cis or trans indolines (I) as described previously in Scheme 1.

SCHEME 2



10

Still another related route to compounds of Formula (I) is shown in Scheme 3. Initiating the synthesis with a nitrobenzene derivative such as (XII), this approach allows for a variety of derivatization. More highly substituted nitrobenzenes can be obtained by traditional synthetic manipulation (*i.e.* aromatic substitution) and are

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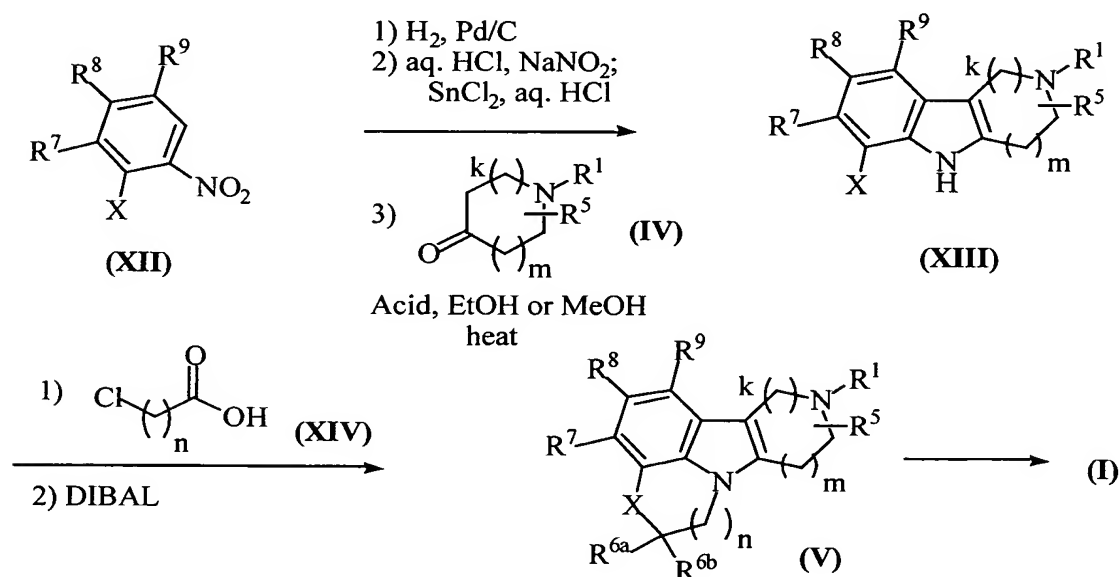
known by those in the art (see Larock, R.C., *Comprehensive Organic Transformations*, VCH Publishers, New York, 1989). Treatment of nitrobenzene derivative with a reducing agent such as LAH, etc., as described previously (see Hudlicky, et. al.), affords the corresponding aniline intermediate. Subsequent

5 formation of the hydrazine followed by Fischer indole cyclization with a suitably functionalized ketone as described above (*i.e.* Scheme 1, (III) to (V)) affords the g-carboline indole (XIII). At this point the fused ring may be appended by condensation of a haloalkyl carboxylic acid or a related activated carboxylic acid (*i.e.* acid chloride, mixed anhydride, etc.) such as (XIV). Reduction of the resultant heterocyclic

10 carbonyl may be effected with various reducing agents, for example, sodium borohydride, diisobutyl aluminum hydride and the like (see Larock, R.C., *Comprehensive Organic Transformations*, VCH Publishers, New York, 1989 and/or Hudlicky, M., "Reductions in Organic Chemistry", Ellis Horwood, Ltd., Chichester, UK, 1984) to afford the tetracyclic indoles (V). Further reduction of the indole (V) to

15 the indolines (I) is as described previously in Scheme 1.

SCHEME 3

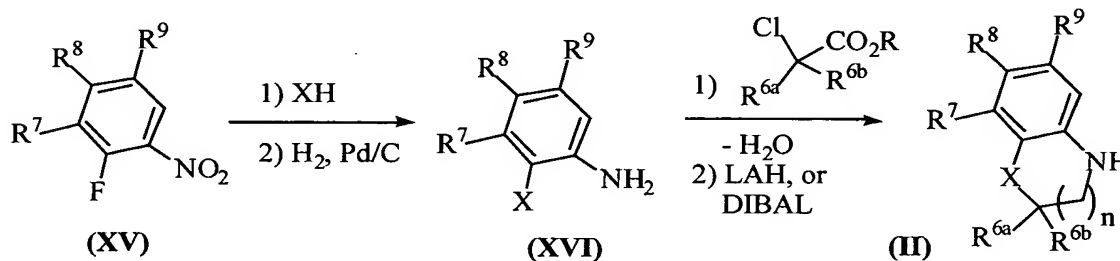


Preparation of the aniline precursors (II) to the Fischer indole cyclizations is

20 shown in Scheme 4. Treatment of a suitably ortho-functionalized aniline (XVI) with

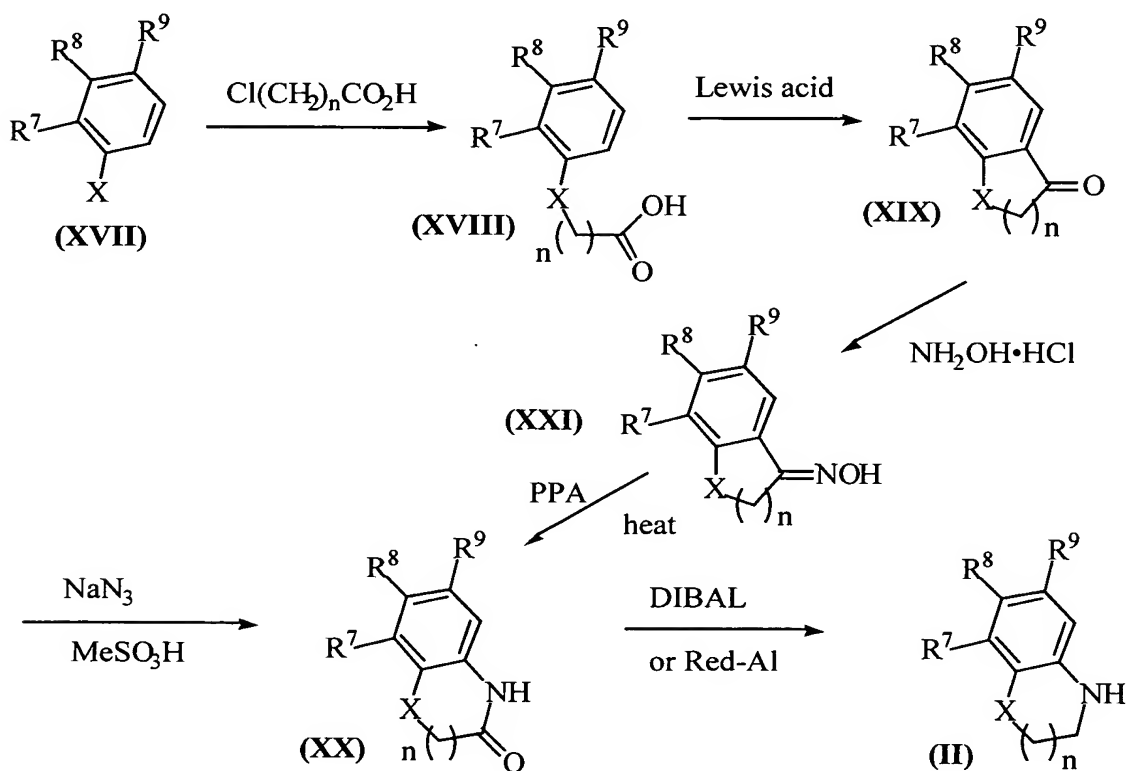
a chloroalkyl carboxylic acid or ester (or equivalent substrate, *i.e.* acrylic acid, acryloyl chloride, etc.) and concomitant condensation, followed by reduction of the resultant heterocyclic carbonyl with a reducing agent such as LAH, DIBAL, or Red-Al affords the fused heterocyclic benzene derivatives (II). More diverse intermediates of (II) may be obtained by formation of the ortho substituted aniline from the corresponding ortho substituted nitobenzenes and concomitant reduction of the nitro moiety as described above. Furthermore, aromatic substitution of the fluoro (or other halo derived nitrobenzene) functionality of (XV) for an oxygen, or sulphur moiety is accomplished, for example, by treatment of (XV) with a nucleophile, such as sodium sulfide or an alcohol, followed by formation of the requisite thiophenol or phenol, respectively, using standard techniques known by those in the art (see Larock, R.C., *Comprehensive Organic Transformations*, VCH Publishers, New York, 1989, page 481). Reduction of the nitro as before affords the substituted anilines (XVI).

SCHEME 4



An alternate approach to the substituted fused anilines (II) is shown in Scheme 5. Treatment of the phenol (X = OH), thiophenol (X = SH), or other nucleophilically aromatic substituted derivative (XVII) with, for example, a haloalkyl carboxylic acid (or equivalent activated haloalkylcarboxylic acid, *i.e.* acid halide, mixed anhydride, acrylic acid, acryloyl chloride, etc.), affords the derivative (XVIII) which when treated under Friedel-Crafts acylation conditions (see Ed. G.A. Olah, "Friedel-Crafts and Related Reactions", J. Wiley and Sons, New York, 1964, Vol 3, Pts 1 and 2 or Chem. Rev., 1955, 229, or Olah, G.A., "Friedel-Crafts Chemistry", Wiley Interscience, New York, 1973, for varying conditions and protocols), *i.e.* strong Lewis acids (AlCl₃, FeCl₃, etc.), affords the cyclic alkylphenones (XIX). Incorporation of the nitrogen

functionality can be accomplished in several ways. For example, Schmidt rearrangement (as described by Smith, P.A.S., *J. Am. Chem. Soc.*, **1948**, 320) is effected by treatment of the carbonyl derivative (XIX) with NaN_3 and methanesulfonic acid to afford the bicyclic lactam (XX). Alternatively, this transformation may be carried out under Hoffmann rearrangement protocol (see, for example, Dike, S.Y., et. al., *Bioorg. Med. Chem. Lett.*, **1991**, 383), by initial formation of the oxime derivative of (XXI) by treatment with hydroxylamine hydrochloride. Subsequent rearrangement to the lactam is efficiently accomplished by heating in polyphosphoric acid to afford the lactam (XX). Reduction of the lactam (XX) can be accomplished with a variety of reducing agents, for example, DIBAL, Red-Al and the like to afford the aniline (II).

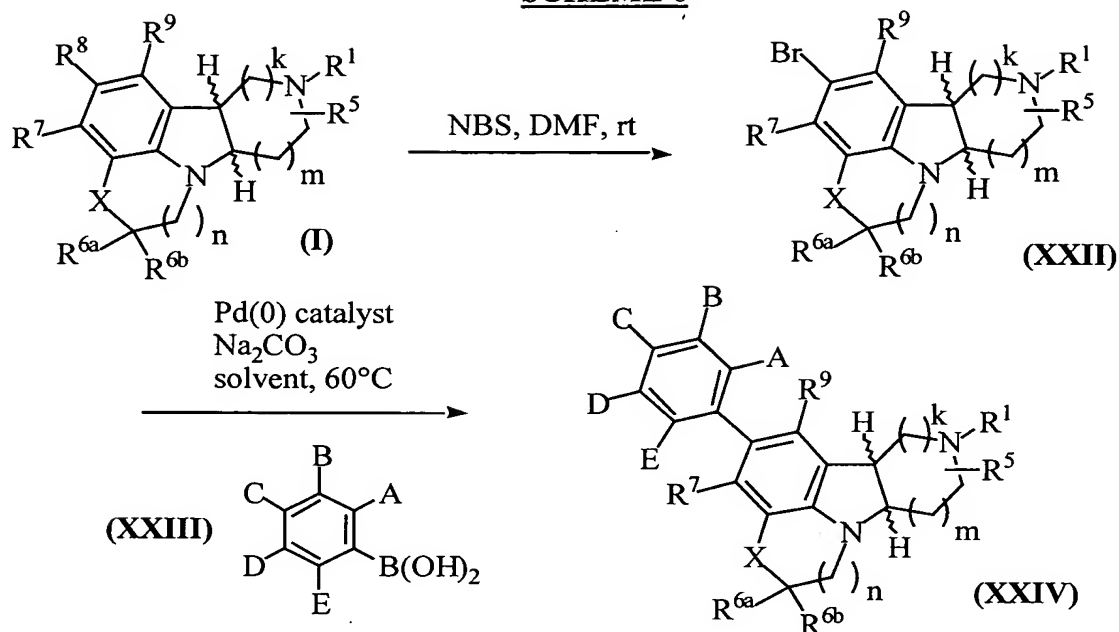
SCHEME 5

The preparation of compounds of Formula (I) with additional diversity of functionalization of the aromatic A ring of the tetracycle is shown in Scheme 6 and

Scheme 7 and described here. Due to the nature of the synthetic route of Scheme 1 to derivatives of Formula (I), compounds with halogen substituents on the A-ring are difficult to prepare. However, bromination of the indolines (I, $R^8 = H$) when the amine is protected, for example, with the Boc or CBZ protecting groups, with, for
5 example, NBS in DMF affords the R^8 brominated derivatives (XXII). These activated aryl derivatives (XXII) act as excellent counterparts for a number of important synthetic transformations.

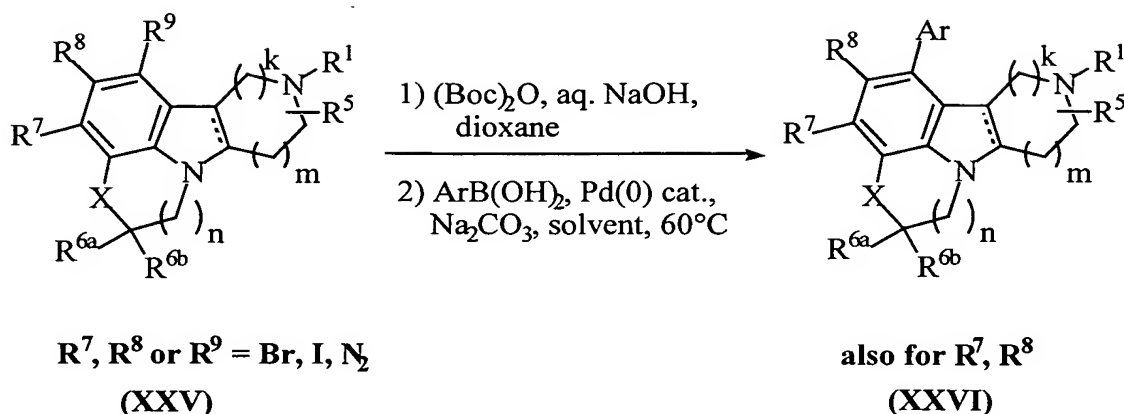
For example, biaryl coupling is accomplished under Suzuki coupling protocol. For a review and leading references of palladium catalyzed cross coupling reactions,
10 see Miyaura, N., Suzuki, A., *Chem. Rev.*, **1995**, 2457. One such procedure entails treatment of the aryl bromide (XXII) with a functionalized aryl boronic acid (XXIII) in the presence of a catalytic Pd(0) species, such as $Pd(PPh_3)_4$, $Pd(PPh_3)_2Cl_2$, $Pd(OAc)_2$, $Pd_2(dba)_3$ and a suitable ligand such as PPh_3 , $AsPh_3$, etc., or other such Pd(0) catalyst, and a base such as Na_2CO_3 or Et_3N in a suitable solvent such as DMF,
15 toluene, THF, DME or the like, to afford the indolines (XXIV). Alternatively formation of the indole boronic acid from the bromine derivative (XXII) (i.e. (I, $R^8 = B(OH)_2$)) would allow for greater diversity in the subsequent coupling of this indole boronic acid with commercially available haloaromatic derivatives in a similar Suzuki coupling strategy as described above to afford the indolines (XXIV).

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SCHEME 6

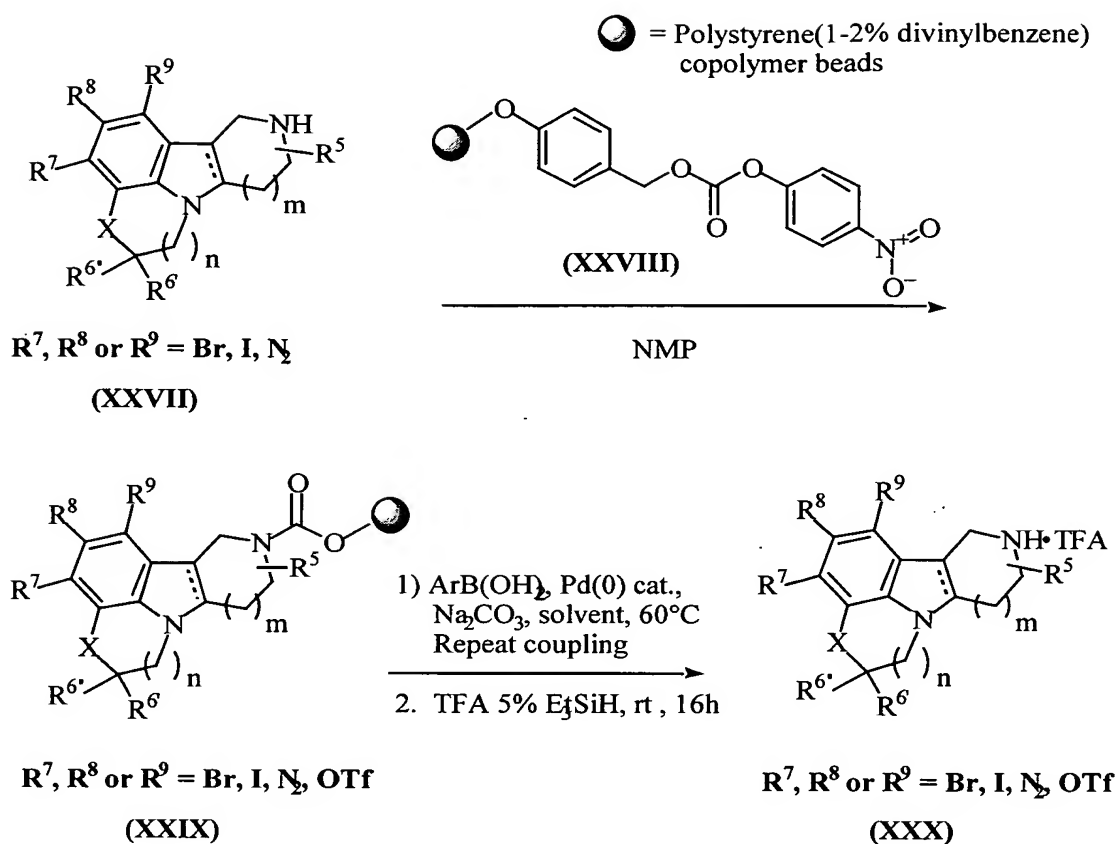
Similarly biaryl coupling of the bromine derivatives (XXV), readily obtained by the synthetic sequence exemplified in Scheme 2, (starting with the suitably functionalized bromo nitrobenzenes (II)), is shown in Scheme 7. This approach allows for the preparation of biaryl indoles as well as the corresponding indoline derivatives. Protection of the amine functionality must be carried out if R¹ = H (see Greene et.al for protections of amines). This is readily accomplished, for example, by treatment of bromo derivatives (XXV) with (Boc)₂O in aqueous sodium hydroxide and dioxane. Subsequent Suzuki coupling with a variety of aryl boronic acids is carried out as described above in Scheme 6, to afford the biaryl adducts (XXVI). This protocol is amenable to R⁷, R⁸, and R⁹ bromide, iodide, triflates, and/or diazo derivatives (see Miyaura, N., Suzuki, A., *Chem. Rev.*, **1995**, 2457, for a review of aryl couplings).

15

SCHEME 7

Furthermore and as an extension of this approach to a rapid preparation of a large array of biaryl indole and indoline derivatives, these bromide derivatives (XXV) can be bound to a solid support and the Suzuki couplings can be carried out on solid support (see XXVIII) as illustrated in Scheme 8. Towards that end treatment of indoline (XXV) with TFA in CH_2Cl_2 , to remove the Boc protecting group, followed extraction from aqueous base provides the free amine (XXXVII). The free amine can be loaded onto a suitable solid support such as (XXVIII) using conditions well known to those skilled in the art. Thus, p-nitrophenylchloroformate Wang resin (XXVIII) which can be obtained commercially from sources such as Novabiochem, Inc. is swollen in a suitable solvent such as N-methyl pyrrolidinone and treated with 1.5 equiv. of amine to afford the functionalized resin (XXIX). Suzuki couplings are then carried out in array format by treatment of resins (XXIX) with a suitable palladium source such as $\text{Pd}(\text{PPh}_3)_4$ or $\text{Pd}(\text{dppf})\text{Cl}_2$ and a suitable base such as 2M aqueous K_2CO_3 or Na_2CO_3 or triethylamine with an excess (typically 5 equivalents) of an aryl boronic acid (procedures for solid-phase Suzuki and other palladium couplings are well-known by those in the art, see for instance L.A. Thompson and J.A. Ellman, *Chem. Rev.* **1996**, *96*, (1), 555-600). The coupling may be repeated to ensure complete conversion to the desired coupled product. Cleavage from the solid support by treatment with TFA affords the corresponding indoles and indolines (XXX) as their TFA salts.

SCHEME 8



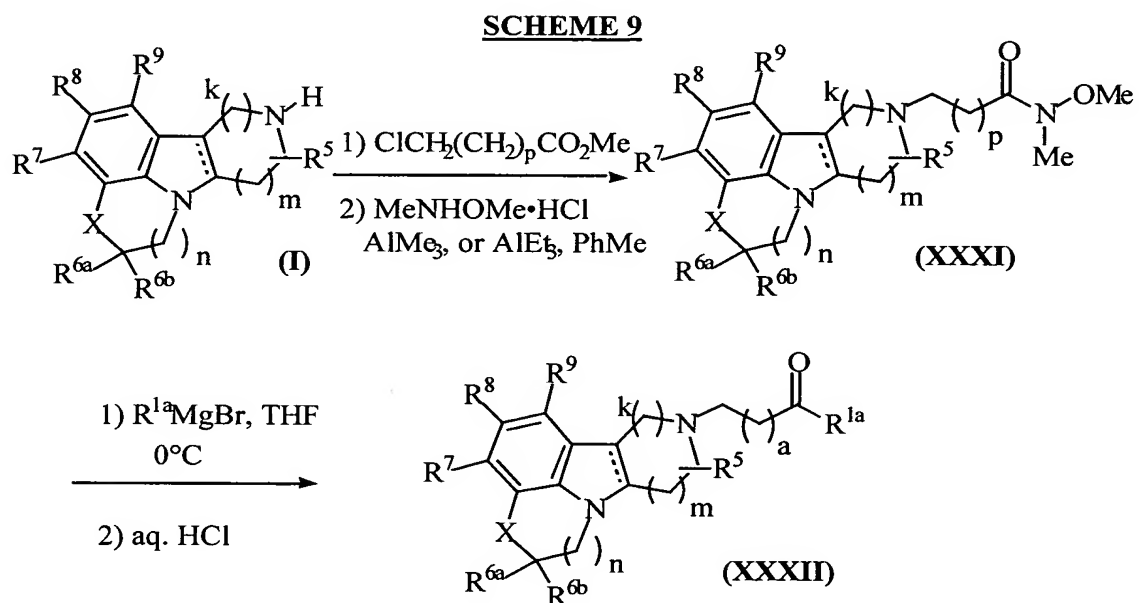
In addition, there exists a wide range of procedures and protocols for functionalizing haloaromatics, aryldiazonium and aryltriflate compounds. These procedures are well known by those in the art and described, for example, by Stanforth, S.P., *Tetrahedron*, **1998**, 263; Buchwald, S.L., et. al., *J. Am. Chem. Soc.*, **1998**, 9722; Stille, J.K., et. al., *J. Am. Chem. Soc.*, **1984**, 7500. Among these procedures are biaryl couplings, alkylations, acylations, aminations, and amidations. The power of palladium catalyzed functionalization of aromatic cores has been explored in depth in the last decade. An excellent review of this field can be found in J. Tsuji, "Palladium Reagents and Catalysts, Innovations in Organic Synthesis", J. Wiley and Sons, New York, **1995**.

One such method to prepare compounds of Formula (I) with substituted R^1 sidechains in a more direct manner is shown in Scheme 9. Alkylation of the indole or indoline derivatives (I, $\text{R}^1 = \text{H}$) with a haloalkyl ester, such as $\text{ClCH}_2(\text{CH}_2)_p\text{CO}_2\text{Me}$,

in the presence of NaI or KI and a base such as K_2CO_3 , Na_2CO_3 or the like, in dioxane or THF or other such solvent while heating (see Glennon, R.A., et. al., *Med. Chem. Res.*, **1996**, 197) affords the R^1 alkylated esters. Subsequent formation of the activated amides (XXXI) is accomplished by treatment of the ester with N,O-

5 dimethylhydroxylamine hydrochloride and a Lewis acid such as trimethylaluminum or triethylaluminum in toluene (see, for example, Golec, J.M.C., et. al., *Tetrahedron*, **1994**, 809) at $0^\circ C$. Treatment of the amide (XXXI) with a variety of organometallic agents, such as Grignard reagents $R^{1a}MgBr$, alkyl and aryl lithium reagents etc. (see Sibi, M.P., et. al., *Tetrahedron Lett.*, **1992**, 1941; and more generally House, H.O.,

10 *Modern Synthetic Reactions*, W.A. Benjamin, Inc., Menlo Park, CA., **1972**), in a suitable solvent such as THF, ether, etc. at low temperatures affords the substituted ketones (XXXII).



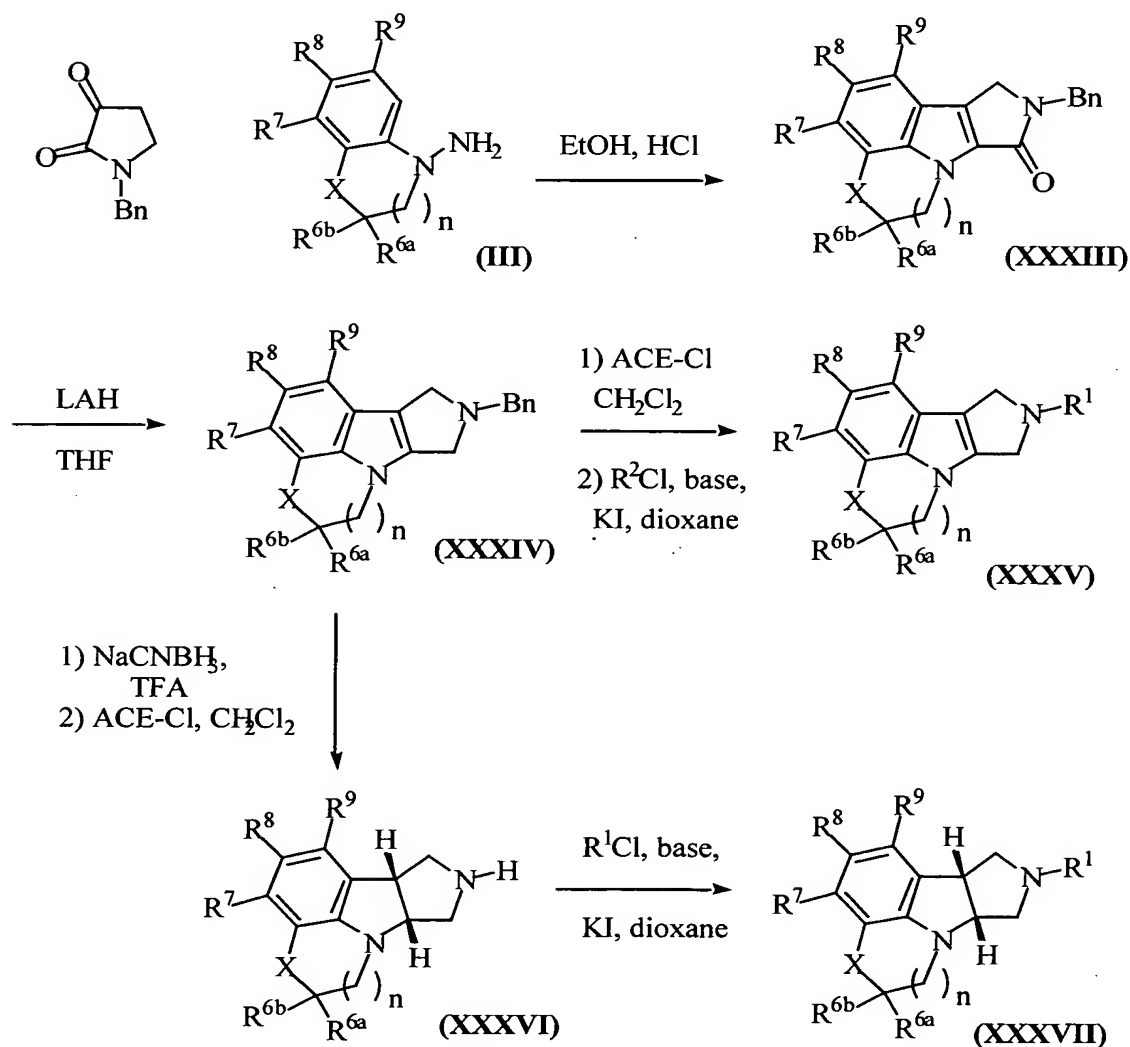
15

Preparation of compounds of Formula (I) where $m=0$, $k=1$ is outlined in Scheme 10 and described here. Fischer indole cyclization of the previously described hydrazine (III) with a known protected 2,3-dioxopyrrolidine (Carlson, E.H., et. al., *J. Org. Chem.*, **1956**, 1087) under a variety of typical cyclization conditions affords the tetracyclic indole (XXXIII). The reduction may be accomplished with a variety of

20 reducing agents, for example, LAH, DIBAL, etc., to yield the pyrole fused indole

(XXXIV). This derivative can then be deprotected and subsequently alkylated as described previously (see Greene, T.W., Wuts, P.G.W., "Protective Groups in Organic Synthesis, 2nd Edition", John Wiley and Sons, Inc., New York, **1991**, and Scheme 1), to give the R¹ alkylated indole analogs (XXXV). Alternatively, reduction of the indole to the indoline, as described previously (see Scheme 1), followed by deprotection of the benzyl group to give (XXXVI) and alkylation gives access to the corresponding R¹ alkylated indoline derivatives (XXXVII). All the previously described methods to functionalize the aromatic ring, and to afford derivatives of varying R¹ sidechains are applicable to these cores.

10

SCHEME 10

EXAMPLES

Chemical abbreviations used in the Examples are defined above. The detailed processes for preparing the compounds of Formula (I) are illustrated by the following Examples. It is, however, understood that this invention is not limited to the specific details of these examples. The Examples as set forth below are intended to demonstrate the scope of the invention but are not intended to limit the scope of the invention. Proton nuclear magnetic resonance spectra (^1H NMR) were measured in chloroform-d (CDCl_3) unless otherwise specified and the peaks are reported in parts per million (ppm) downfield from tetramethylsilane (TMS). The coupling patterns are reported as follows: s, singlet; d, doublet; dd, doublet of doublets; t, triplet; q, quartet; m, multiplet; bs, broad singlet; bm, broad multiplet.

EXAMPLE 1

4,5,7,8,9,10-hexahydropyrido[4,3-*b*]pyrrolo[3,2,1-*hi*]indole hydrochloride

15

A mixture of 1-amino-2,3-dihydroindole (1.0 g, 5.9 mmol), piperidone hydrochloride monohydrate (0.91 g, 5.9 mmol) and isopropanol (29 mL) was brought to reflux for 4 hours. The resulting brown solid was filtered and washed with cold diethylether (20 mL) and dried under vacuum, affording the title compound (1.01 g, 74%). ^1H NMR (CD_3OD , 300 MHz) δ 7.15 (d, 1H, $J = 7.7$ Hz), 6.85-6.96 (m, 2H), 4.39-4.50 (m, 4H), 3.75 (t, 2H, $J = 7.3$ Hz), 3.57 (t, 2H, $J = 6.2$ Hz), 3.15 (t, 2H, $J = 6.2$ Hz) ppm.

20

EXAMPLE 2

9-cyclopropyl-4,5,7,8,9,10-hexahydropyrido[4,3-*b*]pyrrolo[3,2,1-*hi*]indole hydrochloride

25

The title compound was prepared by substituting cyclopropylpiperidone for the monohydrate piperidone hydrochloride by the procedure of Example 1 in 64%. ^1H NMR (DMSO , 300 MHz) δ 7.16 (d, 1H, $J = 7.3$), 7.85-7.93 (m, 2H), 4.6 (d, 1H, J

30

= 6.6), 4.38-4.48 (m, 3H), 3.72-3.85 (m, 1H), 3.7 (t, 2H, J = 7 Hz), 3.58-3.62 (m, 1H), 3.0-3.18 (m, 3H), 1.07-1.12 (m, 2H), 0.83-0.9 (m, 2H) ppm.

EXAMPLE 3

5 (±)-*cis*-4,5,6a,7,8,9,10,10a-octahydropyrido[4,3-*b*]pyrrolo[3,2,1-*hi*]indole

4,5,7,8,9,10-Hexahydropyrido[4,3-*b*]pyrrolo[3,2,1-*hi*]indole from Example 1 (0.50 g, 2.14 mmol) was stirred under N₂ in TFA (15.5 mL) at 0° C for 10 minutes. NaBH₄ (0.44 g, 6.4 mmol) was added slowly keeping the temperature below 2° C.

10 The reaction was allowed to warm to room temperature and stirred overnight. Ice chips were then added and the reaction basified to pH 12 with 50% aqueous NaOH. The aqueous layer was then extracted with CHCl₃ (3 x 20 mL). The combined extracts were washed with brine, H₂O and dried (Na₂SO₄) and evaporated affording the title compound (0.42 g, 100%). ¹H NMR (CDCl₃, 300 MHz) δ 6.94 (d, 1H, J = 7.7 Hz),

15 6.88 (d, 1H, J = 6.9 Hz), 6.63 (t, 7.3, 1H, J = 7.3 Hz), 3.64 (dt, 1H, J = 8.0, 1.5 Hz), 3.29-3.5 (m, 2H), 3.05-3.29 (m, 3H), 3.03 (dd, 1H, J = 11.7, 3.6 Hz), 2.72-3.02 (m, 2H), 1.66-1.90 (m, 2H) ppm.

EXAMPLE 16

20 5,6,8,9,10,11-hexahydro-4*H*-pyrido[3',4':4,5] pyrrolo[3,2,1-*ij*]quinoline

Step A:

1,2,3,4-Tetrahydroquinoline (2.12 g, 15.9 mmol) was dissolved in AcOH (30mL) and water (10 mL). The solution was cooled to 0°C. An aqueous solution of

25 NaNO₂ (1.20g, 17.5 mmol in 3 mL water) was added dropwise. The reaction was warmed to RT and stirred 2 hrs. Water (20mL) and EtOAc (20mL) were added. The layers were separated and the aqueous phase was extracted (2 x 20 mL) with EtOAc. The combined organic layers were washed with brine, dried, and concentrated to afford a crude orange oil (2.62g). The product was purified by column

30 chromatography (20-40% EtOAc/hexane) to afford 1-nitroso-1,2,3,4-tetrahydroquinoline (2.48g, 96%) as a yellow oil. ¹H NMR (CDCl₃, 300MHz) δ 8.07

(d, 1H, J = 8.1 Hz), 7.21-7.34 (m, 3 H), 3.91 (t, 2H, J = 6.2 Hz), 3.81 (t, 2H, J = 6.2 Hz), 1.97-2.05 (m, 2H) ppm.

Step B:

5 1-Nitroso-1,2,3,4-tetrahydroquinoline (1.51 g, 9.0 mmol) was dissolved in THF. The solution was cooled to 0°C. 1M LAH in THF (9 mL, 9.0 mmol) was added dropwise. The reaction was allowed to warm to RT and was stirred over night. The reaction was cooled to 0 °C and was quenched with 20 mL a saturated aqueous Rochelle salt solution (20 mL). The suspension was stirred for 2 h and the layers
10 were separated. The aqueous phase was extracted with EtOAc (3 x 20 mL). The combined organic layers were washed with brine, dried, and concentrated to afford an orange solid (1.26g). The crude product was purified by column chromatography (20-0% hexane/CH₂Cl₂) to afford 1,2,3,4-tetrahydroquinoylamine (1.02g, 76%) as a yellow solid. ¹H NMR (CDCl₃, 300MHz) δ 7.09-7.18 (m, 2H), 6.97 (dd, 1H, J = 0.7
15 Hz, 7.3 Hz), 6.68-6.74 (m, 1H), 3.64 (m, 2H), 3.31 (t, 2H, J = 6.0 Hz), 2.77 (t, 2H, J = 6.6 Hz), 2.02-2.11 (m, 2H) ppm.

Step C:

 1,2,3,4-Tetrahydroquinoylamine (0.925 g, 6.25 mmol) and 4-piperidone
20 monohydrate hydrochloride (0.960g, 6.25 mmol) were dissolved in EtOH (15mL). Conc. HCl (0.52 mL, 6.25 mmol) was added. The reaction was refluxed for 3 hrs and then cooled to RT. The precipitate was collected by vacuum filtration. The residue was washed with 5 mL of EtOH, to afford the title compound (1.32g, 85%) as a pure, white powder. ¹H NMR (CD₃OD, 300MHz) δ 7.22 (d, 1H, J = 8.1 Hz), 6.92-6.97 (m,
25 1H), 6.86 (d, 1H, J = 7.2 Hz), 4.87 (s, 2H), 4.05 (t, 2H, J = 6.0Hz), 3.61 (t, 2H, J = 6.0Hz), 3.14 (t, 2H, J = 6.0Hz), 2.94 (t, 2H, J = 6.3 Hz), 2.16-2.24 (m, 2H) ppm.

EXAMPLE 17**(±)-*cis*-5,6,7a,8,9,10,11,11a-octahydro-4*H*-pyrido[3',4':4,5]pyrrolo[3,2,1-*ij*]quinoline**

5 5,6,8,9,10,11-Hexahydro-4*H*-pyrido[3',4':4,5] pyrrolo[3,2,1-*ij*]quinoline (2.84g, 11.4 mmol) was dissolved in TFA (35 mL). The reaction was cooled to 0°C. NaCNBH₃ (2.15 g, 34.27 mmol) was added in small portions over 30 min, keeping the temperature less than 5°C. The reaction was stirred at 0°C for 2 h. Ice was added to the reaction flask, and the reaction was basified with 50% NaOH until pH=14.

10 Water (20 mL) was added to dissolve the precipitate. The reaction was extracted with CHCl₃ (3 x 20 mL). The combined organic layers were washed with brine, dried, and concentrated to afford the title compound (1.67 g, 68%) as a pale-brown, amorphous solid. ¹H NMR (CDCl₃, 300 MHz) δ 6.80-7.00 (m, 2H), 6.55-6.6.70 (m, 1H), 3.20-3.40 (m, 2H), 2.95-3.20 (m, 2H), 2.75-2.95 (m, 2H), 2.50-2.75 (m, 4H), 2.00-2.20 (m,

15 2H), 1.85-2.00 (m, 1H), 1.70-1.85 (m, 1H) ppm.

EXAMPLE 37**(±)-*cis*-9-(cyclopropylcarbonyl)-4,5,6a,7,8,9,10,10a-octahydropyrido[4,3-*b*]pyrrolo[3,2,1-*hi*]indole**

20 (±)-*cis*-4,5,6a,7,8,9,10,10a-octahydropyrido[4,3-*b*]pyrrolo[3,2,1-*hi*]indole from Example 3 (0.050 g, 0.25 mmol) was dissolved in CH₂Cl₂ (5 mL) with Et₃N (0.75 mL) and cooled to 0°C. The cyclopropanecarbonyl chloride (0.026 g, 0.26 mmol) was then added dropwise. The solution was stirred at 0°C for 1 h and then

25 warmed to room temperature and stirred for 1 h. The reaction mixture was partitioned between water and CHCl₃ (3 x 15 mL) and the layers separated. The aqueous layer was extracted with CHCl₃. The combined organics were washed with brine, H₂O and dried (Na₂SO₄) and evaporated affording a light yellow liquid which was further purified by preparatory silica gel TLC (5% MeOH/ CH₂Cl₂). The title compound

30 was isolated as a clear colorless liquid (0.042g, 65%). ¹H NMR (CD₃OD, 300 MHz)

δ 7.22-7.58 (m, 3H), 4.62-4.75 (m, 1H), 3.85-4.30 (m, 5H), 3.55-3.62 (m, 2H), 1.9-2.18 (m, 3H), 0.75-0.9 (m, 4H) ppm.

EXAMPLE 38

5 (±)-*cis*-9-isobutyryl-4,5,6a,7,8,9,10,10a-octahydropyrido[4,3-*b*]pyrrolo[3,2,1-*hi*]indole

The title compound was prepared by substituting isobutyrylchloride for cyclopropanecarbonyl chloride by the procedure of Example 37 in 53% yield. ¹H
10 NMR (CD₃OD, 300 MHz) δ 6.85-6.95 (m, 2H), 6.6 (t, 1H, J = 7.3), 4.48 (dd, 0.5 H, J = 8.4, 4.0 Hz), 4.21 (br d, 0.5 H, J = 13.2 Hz), 4.05 (dd, 0.5 H, J = 11.7, 4 Hz), 3.85 (br d, 0.5 H, J = 13.9 Hz), 3.47-3.7 (m, 2H), 3.18-3.45 (m, 4H), 2.85-3.18 (m, 3H), 2.72-2.85 (m, 1H), 1.75-2.05 (m, 2H), 1.15 (t, 3H, J = 6.5 Hz), 1.05 (t, 3H, J = 6.9 Hz) ppm.

15

EXAMPLE 89

tert-butyl (±)-*cis*-2-(2-chlorophenyl)-4,5,7,8,10,10a-hexahydropyrido[4,3-*b*]pyrrolo[3,2,1-*hi*]indole-9(6a*H*)-carboxylate

20 Step A:

(±)-*cis*-4,5,6a,7,8,9,10,10a-octahydropyrido[4,3-*b*]pyrrolo[3,2,1-*hi*]indole (387 mg, 1.93 mmol) was dissolved in CHCl₃ (8 mL). BOC₂O (464 mg, 2.13 mmol) was added. The reaction was stirred at RT 18 h. 1M aqueous NaOH (10 mL) was added. The biphasic mixture was stirred 10 min, and the layers were separated. The aqueous
25 phase was extracted with CH₂Cl₂ (3 x 10 mL). The combined organic layers were washed with brine, dried, and concentrated to afford an amorphous white solid (820 mg). The crude product was purified by column chromatography (0-10% MeOH/CH₂Cl₂) to afford *tert*-butyl (±)-*cis*-4,5,7,8,10,10a-hexahydropyrido[4,3-*b*]pyrrolo[3,2,1-*hi*]indole-9(6a*H*)-carboxylate (596 mg, 100%) as an amorphous white
30 solid. ¹H NMR (CDCl₃, 300MHz) δ 6.97 (d, 1H, J = 7.3 Hz), 6.93 (d, 1H, J = 7.3

Hz), 6.60-6.75 (m, 1H), 3.75-3.90 (m, 1H), 3.50-3.72 (m, 1H), 3.05-3.48 (m, 5H), 2.70-2.90 (m, 1H), 1.70-1.90 (m, 2H) ppm. MS (CI, NH₃): 301 (base, M+H)

Step B:

5 To a solution of *tert*-butyl (±)-*cis*-4,5,7,8,10,10a-hexahydropyrido[4,3-*b*]pyrrolo[3,2,1-*hi*]indole-9(6a*H*)-carboxylate (0.576 g, 1.92 mmol) in DMF (4 mL) at 0 °C, freshly recrystallized NBS (0.375 g, 2.1 mmol) was added as a solution in DMF (4 mL). The reaction was stirred at 0 °C for 20 min, after which it was warmed to RT. The reaction was stirred at RT for 0.5 h. Water (10 mL) and EtOAc (10 mL) were
10 added. The layers were separated, and the aqueous phase was extracted with EtOAc (2 x 20 mL). The combined organic layers were washed with brine (2 x 20 mL) and dried. Concentration afforded a crude brown oil. The crude product was purified by column chromatography (MeOH/CH₂Cl₂). *Tert*-butyl (±)-*cis*-2-bromo-4,5,7,8,10,10a-hexahydropyrido[4,3-*b*]pyrrolo[3,2,1-*hi*]indole-9(6a*H*)-carboxylate
15 (550 mg, 75%) was isolated as a brown amorphous solid. ¹H NMR (CDCl₃, 300 MHz) δ 7.06 (s, 1H), 7.02 (s, 1H), 3.70-3.90 (m, 1H), 3.50-3.70 (m, 1H), 3.00-3.45 (m, 6H), 2.70-2.90 (m, 2H), 1.70-1.90 (m, 2H), 1.48 (s, 9H) ppm.

Step C:

20 *Tert*-butyl (±)-*cis*-2-bromo-4,5,7,8,10,10a-hexahydropyrido[4,3-*b*]pyrrolo[3,2,1-*hi*]indole-9(6a*H*)-carboxylate (87.5 mg, 0.23 mmol) was dissolved in benzene (4 mL). 2M sodium carbonate (0.4 mL) added. 2-Chlorophenylboronic acid (71.9 mg, 0.46 mmol) was added, followed by Pd(PPh₃)₂Cl₂ (8.1 mg, 0.0115 mmol). The reaction was evacuated and kept under a nitrogen atmosphere. The suspension
25 was refluxed for 18 h and then cooled to RT. The reaction was concentrated in *vacuo*, after which water (10 mL) and EtOAc (10 mL) were added. The layers were separated and the aqueous phase was extracted with EtOAc (2 x 10 mL). The organic layers were washed with brine (2 x 10 mL), dried, and concentrated to afford a crude brown amorphous solid (110.9mg). The residue was purified by column
30 chromatography (20-40% EtOAc/Hexane) to afford the title compound (62mg, 66%) as a white amorphous solid. MS (CI, NH₃): 411 (base, M+H).

EXAMPLE 90

***tert*-butyl (±)-*cis*-2-(2,4-dichlorophenyl)-4,5,7,8,10,10a-hexahydropyrido[4,3-*b*]pyrrolo[3,2,1-*hi*]indole-9(6a*H*)-carboxylate**

5

The title compound (55.9mg, 50%) was prepared by the method of Example 89 Step C from *tert*-butyl (±)-*cis*-2-bromo-4,5,7,8,10,10a-hexahydropyrido[4,3-*b*]pyrrolo[3,2,1-*hi*]indole-9(6a*H*)-carboxylate (94mg, 0.25 mmol) and 2,4-dichlorophenylboronic acid (95 mg, 0.5 mmol) as a white amorphous solid. MS (CI, NH₃): 445 (base, M+H).

10

EXAMPLE 91

***tert*-butyl (±)-*cis*-2-(3,4-dichlorophenyl)-4,5,7,8,10,10a-hexahydropyrido[4,3-*b*]pyrrolo[3,2,1-*hi*]indole-9(6a*H*)-carboxylate**

15

Tert-butyl (±)-*cis*-2-bromo-4,5,7,8,10,10a-hexahydropyrido[4,3-*b*]pyrrolo[3,2,1-*hi*]indole-9(6a*H*)-carboxylate (135 mg, 0.30 mmol) was dissolved in DME (4 mL). 2M sodium carbonate (0.75 mL) was added. 3,4-Dichlorophenylboronic acid (114 mg, 0.60 mmol) was added, followed by Pd₂(dba)₃ (15 mg, .015 mmol). PPh₃ (16 mg, 0.06 mmol) was added. The reaction flask was degassed and kept under a nitrogen atmosphere. The suspension was refluxed for 18 h cooled to RT. The reaction was concentrated in *vacuo*, after which water (10 mL) and EtOAc (10 mL) were added. The layers were separated and the aqueous phase was extracted with EtOAc (2 x 10 mL). The combined organic layers were washed with brine (2 x 10 mL), dried, and concentrated to afford a crude brown amorphous solid (214 mg). The residue was purified by column chromatography (20-40% EtOAc/Hexane) to afford the title compound (120 mg, 90%) as a white amorphous solid. ¹H NMR (CDCl₃, 300 MHz) δ 7.55 (d, 1H, J = 1.5 Hz), 7.41 (d, 1H, J = 8.4 Hz), 7.30 (dd, 1H, J = 1.8 Hz, 8.4 Hz), 7.26 (s, 1H), 7.13 (s, 1H), 3.75-3.90 (m, 1H), 3.60-3.70 (m, 1H), 3.10-3.50 (m, 7H), 2.80-3.00 (m, 1H), 1.70-1.90 (m, 2H), 1.48 (s, 9H) ppm. MS (CI, NH₃): 445 (base, M+H).

20

25

30

EXAMPLE 92

***tert*-butyl (±)-*cis*-2-(2,3-dichlorophenyl)-4,5,7,8,10,10a-hexahydropyrido[4,3-*b*]pyrrolo[3,2,1-*hi*]indole-9(6a*H*)-carboxylate**

5

The title compound was prepared by the method of Example 90 from *tert*-butyl (±)-*cis*-2-bromo-4,5,7,8,10,10a-hexahydropyrido[4,3-*b*]pyrrolo[3,2,1-*hi*]indole-9(6a*H*)-carboxylate (124 mg, 0.27 mmol) and corresponding 2,3-dichlorophenylboronic acid (104 mg, 0.54 mmol), to afford after chromatographic purification the title compound (157 mg, 99%) as a white amorphous solid. ¹H NMR (CDCl₃, 300 MHz) δ 7.30-7.40 (m, 1H), 7.20 (s, 1H), 7.18 (d, 1H, J = 3.6 Hz), 6.99 (s, 1H), 6.94 (s, 1H), 3.80-3.90 (m, 1H), 3.60-3.80 (m, 1H), 3.10-3.50 (m, 7H), 2.80-3.00 (m, 1H), 1.70-1.90 (m, 2H), 1.47 (s, 9H) ppm. MS (CI, NH₃): 445 (base, M+H).

15

EXAMPLE 93

***tert*-butyl (±)-*cis*-2-[2-chloro-4-(trifluoromethyl)phenyl]-4,5,7,8,10,10a-hexahydropyrido[4,3-*b*]pyrrolo[3,2,1-*hi*]indole-9(6a*H*)-carboxylate**

The title compound was prepared by the method of Example 90 from *tert*-butyl (±)-*cis*-2-bromo-4,5,7,8,10,10a-hexahydropyrido[4,3-*b*]pyrrolo[3,2,1-*hi*]indole-9(6a*H*)-carboxylate (136 mg, 0.30 mmol) and corresponding 2-chloro-4-trifluoromethylphenylboronic acid (128mg, 0.60 mmol), to afford after chromatographic purification the title compound (160 mg, 99%) as a white amorphous solid. ¹H NMR (CDCl₃, 300 MHz) δ 7.70 (br, 1H), 7.51 (dd, 1H, J = 1.1 Hz, 8.0 Hz), 7.42 (d, 1H, J = 8.0 Hz), 7.03 (s, 1H), 6.99 (s, 1H), 3.80-3.90 (m, 1H), 3.60-3.80 (m, 1H), 3.10-3.50 (m, 7H), 2.80-3.00 (m, 1H), 1.70-1.90 (m, 2H), 1.48 (s, 9H) ppm. MS (CI, NH₃): 479 (base, M+H).

25

EXAMPLE 94

***tert*-butyl (\pm)-*cis*-2-(2-chloro-4-methoxyphenyl)-4,5,7,8,10,10a-hexahydropyrido[4,3-*b*]pyrrolo[3,2,1-*hi*]indole-9(6a*H*)-carboxylate**

5 The title compound was prepared by the method of Example 90 from *tert*-butyl (\pm)-*cis*-2-bromo-4,5,7,8,10,10a-hexahydropyrido[4,3-*b*]pyrrolo[3,2,1-*hi*]indole-9(6a*H*)-carboxylate (121 mg, 0.27 mmol) and corresponding 2-chloro-4-methoxyphenylboronic acid (100 mg, 0.54 mmol), to afford after chromatographic purification the title compound (141 mg, 68%) as a white amorphous solid. ¹H NMR (CDCl₃, 300 MHz) δ 7.21 (d, 1H, J = 8.4 Hz), 6.94-6.99 (m, 3H), 6.82 (dd, 1H, J = 2.9 Hz, 8.8 Hz), 3.75-4.00 (m, 7H), 3.60-3.70 (m, 1H), 3.10-3.50 (m, 7H), 2.80-3.00 (m, 1H), 1.70-1.90 (m, 2H), 1.48 (s, 9H) ppm. MS (CI, NH₃): 441 (base, M+H).

EXAMPLE 95

15 ***tert*-butyl (\pm)-*cis*-2-(5-isopropyl-2-methoxyphenyl)-4,5,7,8,10,10a-hexahydropyrido[4,3-*b*]pyrrolo[3,2,1-*hi*]indole-9(6a*H*)-carboxylate**

20 The title compound was prepared by the method of Example 90 from *tert*-butyl (\pm)-*cis*-2-bromo-4,5,7,8,10,10a-hexahydropyrido[4,3-*b*]pyrrolo[3,2,1-*hi*]indole-9(6a*H*)-carboxylate (127 mg, 0.28 mmol) and corresponding 4-isopropyl-2-methoxyphenylboronic acid (109 mg, 0.56 mmol), to afford after chromatographic purification the title compound (58.4 mg, 46%) as a white amorphous solid. ¹H NMR (CDCl₃, 300 MHz) δ 7.00-7.20 (m, 4H), 6.87 (d, 1H, J = 8.4 Hz), 3.85-4.0 (m, 1H), 3.79 (s, 3H), 3.60-3.75 (m, 1H), 3.10-3.50 (m, 6H), 2.70-3.00 (m, 2H), 1.70-1.90 (m, 2H), 1.48 (s, 9H), 1.25 (d, 6 H, J = 7.0 Hz) ppm. MS (CI, NH₃): 449 (base, M+H).

25

EXAMPLE 96

***tert*-butyl (±)-*cis*-2-(3-fluorophenyl)-4,5,7,8,10,10a-hexahydropyrido[4,3-*b*]pyrrolo[3,2,1-*hi*]indole-9(6a*H*)-carboxylate**

5 The title compound was prepared by the method of Example 90 *tert*-butyl (±)-*cis*-2-bromo-4,5,7,8,10,10a-hexahydropyrido[4,3-*b*]pyrrolo[3,2,1-*hi*]indole-9(6a*H*)-carboxylate (125 mg, 0.28 mmol) and corresponding 3-fluorophenylboronic acid (77 mg, 0.56 mmol), to afford after chromatographic purification the title compound (48 mg, 44%) as a white amorphous solid. ¹H NMR (CDCl₃, 300 MHz) δ 7.20-7.40 (m, 2H), 7.10-7.20 (m, 3H), 6.80-7.00 (m, 1H), 3.80-3.90 (m, 1H), 3.60-3.80 (m, 1H), 3.10-3.50 (m, 7H), 2.80-3.00 (m, 1H), 1.70-1.90 (m, 2H), 1.48 (s, 9H) ppm. MS (CI, NH₃): 395 (base, M+H).

EXAMPLE 97

15 ***tert*-butyl (±)-*cis*-2-(2,4-dimethoxyphenyl)-4,5,7,8,10,10a-hexahydropyrido[4,3-*b*]pyrrolo[3,2,1-*hi*]indole-9(6a*H*)-carboxylate**

 The title compound was prepared by the method of Example 90 from *tert*-butyl (±)-*cis*-2-bromo-4,5,7,8,10,10a-hexahydropyrido[4,3-*b*]pyrrolo[3,2,1-*hi*]indole-9(6a*H*)-carboxylate (143 mg, 0.32 mmol) and corresponding 2,4-dimethoxyphenylboronic acid (115 mg, 0.63 mmol), to afford after chromatographic purification the title compound (92 mg, 66%) as a white amorphous solid. ¹H NMR (CDCl₃, 300 MHz) δ 7.15-7.18 (m, 1H), 7.08 (s, 1H), 7.04 (s, 1H), 6.40-6.60 (m, 2H), 3.75-4.00 (m, 7H), 3.60-3.70 (m, 1H), 3.00-3.50 (m, 7H), 2.70-2.90 (m, 1H), 1.70-1.90 (m, 2H), 1.48 (s, 9H) ppm. MS (CI, NH₃): 437 (base, M+H).

EXAMPLE 98

(±)-cis-2-(2-chlorophenyl)-4,5,6a,7,8,9,10,10a-octahydropyrido[4,3-b]pyrrolo[3,2,1-*hi*]indole

5 *Tert*-butyl (±)-*cis*-2-(2-chlorophenyl)-4,5,7,8,10,10a-hexahydropyrido[4,3-
b]pyrrolo[3,2,1-*hi*]indole-9(6a*H*)-carboxylate (45.1 mg, 0.11 mmol) was dissolved in
 20% TFA in methylene chloride (4mL) and was stirred at RT for 2 h. The reaction
 was solution was cooled to 0 °C and basified with 1M NaOH until pH > 14. The
 layers were separated. The aqueous phase was extracted the methylene chloride (2 x
 10 10 ml). The organic layers were washed with brine and dried. Concentration afforded
 the title compound (29.3 mg, 86%) as a pale yellow amorphous solid. ¹H NMR
 (CDCl₃, 300 MHz) δ 7.42 (dd, 1H, J = 1.4, 7.3 Hz), 7.16-7.33 (m, 3H), 7.02 (s, 1H),
 6.96 (s, 1H), 3.69 (dt, 1H, J = 1.4, 8.1 Hz), 3.15-3.50 (m, 5H), 3.06 (dt, 1H, J = 3.2,
 12.3 Hz), 2.82-2.97 (m, 3H), 1.78-1.93 (m, 2H) ppm. MS (CI, NH₃): 311 (base,
 15 M+H).

EXAMPLE 99

(±)-cis-2-(2,4-dichlorophenyl)-4,5,6a,7,8,9,10,10a-octahydropyrido[4,3-b]pyrrolo[3,2,1-*hi*]indole

20 The title compound was prepared by the method of Example 98 from *tert*-
 butyl (±)-*cis*-2-(2,4-dichlorophenyl)-4,5,7,8,10,10a-hexahydropyrido[4,3-
b]pyrrolo[3,2,1-*hi*]indole-9(6a*H*)-carboxylate (44.3 mg, 0.99mmol) to afford the title
 compound (35mg, 100%) as a pale yellow amorphous solid. The enantiomers of (±)-
 25 *cis*-2-(2,4-dichlorophenyl)-4,5,6a,7,8,9,10,10a-octahydropyrido[4,3-*b*]pyrrolo[3,2,1-
hi]indole were separated by preparative HPLC on a chiracel OD column using
 isocratic 6% IPA/hexane as the eluent. ¹H NMR (CDCl₃, 300 MHz) δ 7.44 (s, 1H),
 7.23-7.26 (m, 2H), 6.97 (s, 1H), 6.92 (s, 1H), 3.70 (dt, 1H, J = 1.4, 8.0 Hz), 3.15-3.50
 (m, 5H), 3.06 (dt, 1H, J = 3.3, 11.3 Hz), 2.77-2.96 (m, 3H), 1.76-1.93 (m, 2H) ppm.
 30 MS (CI, NH₃): 345 (base, M+H).

EXAMPLE 100

**(±)-cis-2-(3,4-dichlorophenyl)-4,5,6a,7,8,9,10,10a-octahydropyrido[4,3-
b]pyrrolo[3,2,1-*hi*]indole**

5 The title compound was prepared by the method of Example 98 from *tert*-butyl (±)-cis-2-(3,4-dichlorophenyl)-4,5,7,8,10,10a-hexahydropyrido[4,3-
b]pyrrolo[3,2,1-*hi*]indole-9(6a*H*)-carboxylate (110 mg, 0.25mmol) to afford the title
compound (71mg, 82%) as a pale yellow amorphous solid. ¹H NMR (CDCl₃, 300
10 MHz) δ 7.57 (d, 1H, J = 2.2 Hz), 7.41 (d, 1H, J = 8.4 Hz), 7.30 (dd, 1H, J = 1.8, 8.1
Hz), 7.13 (s, 1H), 7.07 (s, 1H), 3.70 (dt, 1H, J = 1.8, 7.6 Hz), 3.15-3.50 (m, 5H), 3.04
(dt, 1H, J = 3.6, 12.4 Hz), 2.83-2.95 (m, 3H), 1.76-1.92 (m, 2H) ppm. MS (CI, NH₃):
345 (base, M+H).

EXAMPLE 101

15 **(±)-cis-2-(2,3-dichlorophenyl)-4,5,6a,7,8,9,10,10a-octahydropyrido[4,3-
b]pyrrolo[3,2,1-*hi*]indole**

 The title compound was prepared by the method of Example 98 from *tert*-butyl (±)-cis-2-(2,3-dichlorophenyl)-4,5,7,8,10,10a-hexahydropyrido[4,3-
20 b]pyrrolo[3,2,1-*hi*]indole-9(6a*H*)-carboxylate (128 mg, 0.29 mmol) to afford the title
compound (99mg, 100%) as a pale yellow amorphous solid. The enantiomers were
separated by preparative HPLC on a chiracel OD column using isocratic 6%
IPA/hexane as the eluent. ¹H NMR (CDCl₃, 300 MHz) δ 7.38 (dd, 1H, J = 2.6, 7.3
Hz), 7.14-7.23 (m, 2H), 7.02 (s, 1H), 6.98 (s, 1H), 6.92 (s, 1H), 3.70 (dt, 1H, J = 1.8,
25 8.1 Hz), 3.15-3.50 (m, 5H), 3.05 (dt, 1H, J = 3.3, 12.2 Hz), 2.85-2.95 (m, 3H), 1.73-
1.93 (m, 2H) ppm. MS (CI, NH₃): 345 (base, M+H).

EXAMPLE 102

(±)-cis-2-[2-chloro-4-(trifluoromethyl)phenyl]-4,5,6a,7,8,9,10,10a-octahydropyrido[4,3-*b*]pyrrolo[3,2,1-*h*]indole

The title compound was prepared by the method of Example 98 *tert*-butyl (\pm)-*cis*-2-[2,-chloro-4-(trifluoromethyl)phenyl]-4,5,7,8,10,10a-hexahydropyrido[4,3-*b*]pyrrolo[3,2,1-*hi*]indole-9(6a*H*)-carboxylate (80 mg, 0.17 mmol) to afford the title compound (65.3 mg, 100%) as a pale yellow amorphous solid. The enantiomers were separated by preparative HPLC on a chiracel OD column using isocratic 3% IPA/hexane as the eluent. ^1H NMR (CDCl_3 , 300 MHz) δ 7.69 (s, 1H), 7.51 (d, 1H, $J = 8.1\text{Hz}$), 7.42 (d, 1H, $J = 8.0\text{ Hz}$), 7.02 (s, 1H), 6.96 (s, 1H), 3.68-3.73 (m, 1H), 3.16-3.50 (m, 5H), 2.85-3.09 (m, 4H), 1.75-1.93 (m, 2H) ppm. MS (CI, NH_3): 379 (base, $\text{M}+\text{H}$).

15

EXAMPLE 103

(±)-cis-2-(2-chloro-4-methoxyphenyl)-4,5,6a,7,8,9,10,10a-octahydropyrido[4,3-*b*]pyrrolo[3,2,1-*hi*]indole

The title compound was prepared by the method of Example 98 from *tert*-butyl (±)-*cis*-2-(2-chloro-4-methoxyphenyl)-4,5,7,8,10,10a-hexahydropyrido[4,3-*b*]pyrrolo[3,2,1-*hi*]indole-9(6a*H*)-carboxylate (60 mg, 0.14 mmol) to afford the title compound (50.4 mg, 100%) as a pale yellow amorphous solid. ¹H NMR (CDCl₃, 300 MHz) δ 7.22 (d, 1H, J = 8.8 Hz), 6.95-7.00 (m, 2H), 7.02 (s, 1H), 6.92 (s, 1H), 6.81 (dd, 1H, J = 2.7, 8.5 Hz), 3.82 (s, 3H), 3.69 (dt, 1H, J = 1.4, 7.7 Hz), 3.13-3.50 (m, 5H), 3.00-3.10 (dt, 1H, J = 3.3, 11.7 Hz), 2.84-2.94 (m, 3H), 1.74-1.92 (m, 2H) ppm. MS (CI, NH₃): 341 (base, M+H).

EXAMPLE 104

(±)-*cis*-2-(4-isopropyl-2-methoxyphenyl)-4,5,6a,7,8,9,10,10a-octahydropyrido[4,3-*b*]pyrrolo[3,2,1-*hi*]indole

5 The title compound was prepared by the method of Example 98 from *tert*-butyl (±)-*cis*-2-(4-isopropyl-2-methoxyphenyl)-4,5,7,8,10,10a-hexahydropyrido[4,3-*b*]pyrrolo[3,2,1-*hi*]indole-9(6a*H*)-carboxylate (52 mg, 0.12 mmol) to afford the title compound (42 mg, 100%) as a pale yellow amorphous solid. ¹H NMR (CDCl₃, 300 MHz) δ 7.07-7.14 (m, 4H), 6.88 (d, 1H, J = 8.4 Hz), 3.79 (s, 3H), 3.68 (dt, 1H, J =
10 1.4, 8.0 Hz), 3.14-3.50 (m, 5H), 3.05 (dt, 1H, J = 3.3, 12.1 Hz), 2.79-2.94 (m, 3H), 1.60-1.93 (m, 3H), 1.25 (d, 6H, J = 6.9 Hz) ppm. MS (CI, NH₃): 349 (base, M+H).

EXAMPLE 105

15 **(±)-*cis*-2-(3-fluorophenyl)-4,5,6a,7,8,9,10,10a-octahydropyrido[4,3-*b*]pyrrolo[3,2,1-*hi*]indole**

 The title compound was prepared by the method of Example 98 from *tert*-butyl (±)-*cis*-2-(3-fluorophenyl)-4,5,7,8,10,10a-hexahydropyrido[4,3-*b*]pyrrolo[3,2,1-*hi*]indole-9(6a*H*)-carboxylate (39.5 mg, 0.10 mmol) to afford the title compound (35.4
20 mg, 90%) as a pale yellow amorphous solid. The enantiomers were separated by preparative HPLC on a chiracel OD column using isocratic 5% IPA/hexane as the eluent. ¹H NMR (CDCl₃, 300 MHz) δ 7.19-7.35 (m, 3H), 7.16 (s, 1H), 7.11 (s, 1H), 6.89-6.96 (m, 1H), 3.69 (dt, 1H, J = 1.8, 8.0 Hz), 3.15-3.50 (m, 5H), 3.04 (dt, 1H, J = 3.3, 12.1 Hz), 2.83-2.95 (m, 3H), 1.76-1.92 (m, 2H) ppm. MS (CI, NH₃): 295 (base,
25 M+H).

EXAMPLE 106

(±)-cis-2-(2,4-dimethoxyphenyl)-4,5,6a,7,8,9,10,10a-octahydropyrido[4,3-*b*]pyrrolo[3,2,1-*hi*]indole

5 The title compound was prepared by the method of Example 98 from *tert*-butyl (±)-cis-2-(2,4-dimethoxyphenyl)-4,5,7,8,10,10a-hexahydropyrido[4,3-*b*]pyrrolo[3,2,1-*hi*]indole-9(6a*H*)-carboxylate (85.0 mg, 0.19 mmol) to afford the title compound (55.0 mg, 86%) as a pale yellow amorphous solid. The enantiomers were separated by preparative HPLC on a chiracel OD column using isocratic 8% IPA/hexane as the eluent. ¹H NMR (CDCl₃, 300 MHz) δ 7.17 (dd, 1H, J = 1.4, 6.9 Hz), 7.06 (s, 1H), 7.01 (s, 1H), 6.50-6.60 (m, 2H), 3.84 (s, 3H), 3.79 (s, 3H), 3.67 (dt, 1H, J = 1.5, 7.7 Hz), 3.12-3.49 (m, 5H), 3.05 (dt, 1H, J = 3.3, 12.1 Hz), 2.78-2.98 (m, 3H), 1.73-1.91 (m, 2H) ppm. MS (CI, NH₃): 337 (base, M+H).

15

EXAMPLE 107

***tert*-butyl (±)-cis-5,6,8,9,11,11a-hexahydro-4*H*-pyrido[3',4':4,5]pyrrolo[3,2,1-*ij*]quinoline-10(7a*H*)-carboxylate**

(±)-Cis-5,6,7a,8,9,10,11,11a-octahydro-4*H*-pyrido[3',4':4,5]pyrrolo[3,2,1-*ij*]quinoline, from Example 17 (1.67 g, 7.79 mmol) was dissolved in dioxane (16 mL) and 1M NaOH (8 mL). The reaction was cooled to 0°C. BOC₂O (1.87 g, 8.57 mmol) was added. The reaction was stirred at RT 18 hrs. EtOAc (10 mL) was added and the biphasic mixture was stirred for 10 min. the layers were separated. The aqueous phase was extracted with EtOAc (3 x 10 mL). The combined organic layers were washed with brine, dried, and concentrated to afford an amorphous white solid (2.30 g). The crude product was purified by column chromatography (20-40% EtOAc/hexane) to afford the title compound (2.17 g, 69%) as an amorphous white solid. ¹H NMR (CDCl₃, 300MHz) δ 6.93 (d, 1H, J = 7.3 Hz), 6.86 (d, 1H, J = 7.3 Hz), 6.61-6.66 (m, 1H), 3.65-3.80 (m, 1H), 3.30-3.50 (m, 1H), 3.10-3.31 (m, 3H), 2.70 (t, 2H, J = 6.6 Hz), 2.50-2.65 (m, 1H), 2.00-2.20 (m, 2H), 1.75-1.90 (m, 2H) ppm. MS (CI, NH₃): 315 (base, M+H)

EXAMPLE 108

***tert*-butyl (±)-*cis*-2-bromo-5,6,8,9,11,11a-hexahydro-4*H*-
pyrido[3',4':4,5]pyrrolo[3,2,1-*ij*]quinoline-10(7*aH*)-carboxylate**

5

The title compound (0.81 g, 35%) was prepared by the method of Example 89 Step B using *tert*-butyl (±)-*cis*-5,6,8,9,11,11a-hexahydro-4*H*-pyrido[3',4':4,5]pyrrolo[3,2,1-*ij*]quinoline-10(7*aH*)-carboxylate (1.85 g) as an amorphous white solid. ¹H NMR (CDCl₃, 300 MHz) δ 7.01 (s, 1H), 6.98 (s, 1H),
10 3.50-3.70 (m, 1H), 3.30-3.50 (m, 1H), 3.00-3.30 (m, 5H), 2.50-2.70 (m, 3H), 2.00-2.30 (m, 2H), 1.70-1.90 (m, 2H), 1.48 (s, 9H) ppm.

EXAMPLE 109

***tert*-butyl (±)-*cis*-2-(2,3-dichlorophenyl)-5,6,8,9,11,11a-hexahydro-4*H*-
pyrido[3',4':4,5]pyrrolo[3,2,1-*ij*]quinoline-10(7*aH*)-carboxylate**

15

Tert-butyl (±)-*cis*-2-bromo-5,6,8,9,11,11a-hexahydro-4*H*-pyrido[3',4':4,5]pyrrolo[3,2,1-*ij*]quinoline-10(7*aH*)-carboxylate (110 mg, 0.28 mmol) was dissolved in DME (4 mL). 2M aqueous sodium carbonate (0.75 ml) was added.
20 2,3-Dichlorophenylboronic acid (107 mg, 0.56 mmol) was added, followed by Pd₂(dba)₃ (14.5 mg, .014 mmol). P(Ph)₃ (14.7 mg, 0.056 mmol) was added. The reaction flask was degassed and kept under a nitrogen atmosphere. The suspension was refluxed for 18 h cooled to rt. The reaction was concentrated in *vacuo*, after which water (10 mL) and EtOAc (10 mL) were added. The layers were separated and
25 the aqueous phase was extracted with EtOAc (2 x 10 mL). The combined organic layers were washed with brine (2 x 10 mL), dried, and concentrated to afford a crude brown amorphous solid (162 mg). The residue was purified by column chromatography (20-0% hexane/CH₂Cl₂) to afford the title compound (96.8 mg, 75%) as a white amorphous solid. ¹H NMR (CDCl₃, 300 MHz) δ 7.61-7.94 (m, 1H),
30 7.20 (s, 1 H), 7.18 (d, 1H, 3.3 Hz), 7.00 (s, 1H), 6.93 (s, 1H), 3.70-3.74 (m, 1H), 3.45-

60 (m, 1H), 3.15-3.35 (m, 4H), 2.65-2.80 (m, 4H), 2.10-2.20 (m, 2H), 1.80-2.00 (m, 2H), 1.46 (s, 9H) ppm.

EXAMPLE 110

5 ***tert*-butyl (±)-*cis*-2-(3,4-dichlorophenyl)-5,6,8,9,11,11a-hexahydro-4*H*-pyrido[3',4':4,5]pyrrolo[3,2,1-*ij*]quinoline-10(7*aH*)-carboxylate**

The title compound was prepared by the method of Example 109 from *tert*-butyl (±)-*cis*-2-bromo-5,6,8,9,11,11a-hexahydro-4*H*-pyrido[3',4':4,5]pyrrolo[3,2,1-*ij*]quinoline-10(7*aH*)-carboxylate (101.7 mg, 0.26 mmol) and 3,4-dichlorophenylboronic acid (97 mg, 0.52 mmol), after chromatographic purification (91.6 mg, 77%) as a white amorphous solid. ¹H NMR (CDCl₃, 300 MHz) δ 7.57 (d, 1H, J = 1.8 Hz), 7.42 (d, 1H, J = 8.4 Hz), 7.31 (dd, 1H, J = 2.2, 8.4 Hz), 7.12 (bs, 1H), 7.07 (bs, 1H), 3.62-3.75 (m, 1H), 3.48-60 (m, 1H), 3.15-3.35 (m, 4H), 2.65-2.80 (m, 4H), 2.10-2.20 (m, 2H), 1.85-2.00 (m, 2H), 1.46 (s, 9H) ppm.

EXAMPLE 111

20 ***tert*-butyl (±)-*cis*-2-[2-chloro-4-(trifluoromethyl)phenyl]-5,6,8,9,11,11a-hexahydro-4*H*-pyrido[3',4':4,5]pyrrolo[3,2,1-*ij*]quinoline-10(7*aH*)-carboxylate**

The title compound was prepared by the method of Example 109 from *tert*-butyl (±)-*cis*-2-bromo-5,6,8,9,11,11a-hexahydro-4*H*-pyrido[3',4':4,5]pyrrolo[3,2,1-*ij*]quinoline-10(7*aH*)-carboxylate (63 mg, 0.16 mmol) and 2-chloro-4-(trifluoromethyl)phenylboronic acid (69 mg, 0.32 mmol), after chromatographic purification (35.9 mg, 46%) as a white amorphous solid. ¹H NMR (CDCl₃, 300 MHz) δ 7.69 (s, 1H), 7.51 (bd, 1H, J = 8.0 Hz), 7.42 (d, 1H, J = 8.1 Hz), 7.04 (s, 1H), 6.97 (s, 1H), 3.60-3.75 (m, 1H), 3.48-60 (m, 1H), 3.15-3.35 (m, 4H), 2.65-2.80 (m, 4H), 2.10-2.20 (m, 2H), 1.85-2.00 (m, 2H), 1.46 (s, 9H) ppm. MS (CI, NH₃): 493 (base, M+H).

30

EXAMPLE 112

(±)-cis-2-(2,3-dichlorophenyl)-5,6,7a,8,9,10,11,11a-octahydro-4H-pyrido[3',4':4,5]pyrrolo[3,2,1-ij]quinoline

5 *Tert*-butyl (±)-cis-2-(2,3-dichlorophenyl)-5,6,8,9,11,11a-hexahydro-4*H*-pyrido[3',4':4,5]pyrrolo[3,2,1-*ij*]quinoline-10(7*aH*)-carboxylate (55 mg, 0.12 mmol) was dissolved in 20% TFA in methylene chloride (4mL) and was stirred at RT for 2 h. The reaction was solution was cooled to 0 °C and basified with 1M NaOH until pH > 14. The layers were separated. The aqueous phase was extracted the methylene
10 chloride (2 x 10 ml). The organic layers were washed with brine and dried. Concentration afforded the title compound (43 mg, 100%) as a pale yellow amorphous solid. ¹H NMR (CDCl₃, 300 MHz) δ 7.37 (dd, 1H, J = 2.6, 7.3 Hz), 7.15-7.23 (m, 2 H), 6.97 (s, 1H), 6.92 (s, 1H), 3.43-3.46 (m, 1H), 3.31 (dt, 1H, J = 4.4, 10.2), 3.03-3.11 (m, 2H), 2.81-2.94 (m, 2H), 2.60-2.80 (m, 4H), 2.11-2.20 (m, 2H),
15 1.89-1.98 (m, 1H), 1.74-1.85 (m, 1H) ppm. MS (CI, NH₃): 359 (base, M+H).

EXAMPLE 113

(±)-cis-2-(3,4-dichlorophenyl)-5,6,7a,8,9,10,11,11a-octahydro-4H-pyrido[3',4':4,5]pyrrolo[3,2,1-ij]quinoline

20 The title compound (72.6 mg, 100%) was prepared by the method of Example 112 from *tert*-butyl (±)-cis-2-(3,4-dichlorophenyl)-5,6,8,9,11,11a-hexahydro-4*H*-pyrido[3',4':4,5]pyrrolo[3,2,1-*ij*]quinoline-10(7*aH*)-carboxylate (90 mg, 0.20 mmol) as pale yellow amorphous solid. ¹H NMR (CDCl₃, 300 MHz) δ 7.58 (d, 1H, J = 2.2 Hz), 7.41 (d, 1 H, J = 8.4 Hz), 7.32 (dd, 1H, J = 2.2, 8.4 Hz), 7.09 (s, 1H), 7.07 (s, 1H), 3.34-3.46 (m, 1H), 3.31 (dt, 1H, J = 4.4, 10.7 Hz), 3.03-3.13 (m, 2H), 2.83-2.92 (m, 2H), 2.61-2.78 (m, 4H), 2.10-2.19 (m, 2H), 1.74-1.91 (m, 2H) ppm. MS (CI, NH₃): 359 (base, M+H).

EXAMPLE 114

(±)-*cis*-2-[2-chloro-4-(trifluoromethyl)phenyl]-5,6,7a,8,9,10,11,11a-octahydro-4*H*-pyrido[3',4':4,5]pyrrolo[3,2,1-*ij*]quinoline

- 5 The title compound (21 mg, 90%) was prepared by the method of Example 112 from *tert*-butyl (±)-*cis*-2-(3,4-dichlorophenyl)-5,6,8,9,11,11a-hexahydro-4*H*-pyrido[3',4':4,5]pyrrolo[3,2,1-*ij*]quinoline-10(7a*H*)-carboxylate (28.5 mg, 0.06 mmol) as a pale yellow amorphous solid. The enantiomers of the title compound were separated by preparative HPLC on a Chiracel OD column using isocratic 6% IPA/hexane as the eluent. ¹H NMR (CDCl₃, 300 MHz) δ 7.46 (s, 1H), 7.69 (s, 1H), 7.49 (d, 1H, J = 8.0 Hz), 7.43 (d, 1H, J = 8.08 Hz), 7.02 (s, 1H), 6.96 (s, 1H), 3.45-3.50 (m, 1H), 3.32 (dt, 1H, J = 4.4, 10.3 Hz), 3.01-3.12 (m, 2H), 2.84-2.89 (m, 2H), 2.64-2.81 (m, 4H), 2.11-2.23 (m, 2H), 1.90-1.98 (m, 1H), 175-1.86 (m, 1H) ppm. MS (CI, NH₃): 393 (base, M+H).

15

EXAMPLE 189

4-((±)-*cis*-2-(2-chlorophenyl)-4,5,7,8,10,10a-hexahydropyrido[4,3-*b*]pyrrolo[3,2,1-*hi*]indol-9(6a*H*)-yl)-1-(4-fluorophenyl)-1-butanone

- 20 (±)-*Cis*-2-(2-chlorophenyl)-4,5,6a,7,8,9,10,10a-octahydropyrido[4,3-*b*]pyrrolo[3,2,1-*hi*]indole (26.4 mg, 0.085 mmol) 0.7 ml of MEK. KI (14 mg, 0.085 mmol) and K₂CO₃ (22 mg, 0.26 mmol), and 4-chloro-4'-fluorobutyrophenone (22.2 mg, 0.11 mmol) were added. The suspension was refluxed for 48 h and then cooled to rt. The suspension was filtered and the residue was washed with CH₂Cl₂ (5 ml).
- 25 The solution was concentrated in vacuo. The residue was purified by column chromatography (10% MeOH-CH₂Cl₂) to afford the title compound (18.8 mg, 47%) as a white amorphous solid. ¹H NMR (CDCl₃, 300 MHz) δ 8.00-8.04 (m, 2 H), 7.41 (dd, 1H, J = 1.5, 7.3 Hz), 7.30 (dd, 1H, J = 1.8, 7.3 Hz), 7.10-7.20 (m, 4H), 7.01 (s, 1H), 6.96 (s, 1H), 3.68 (bt, 1H, J = 6.6 Hz), 3.30-3.50 (m, 2H), 3.10-3.30 (m, 2H), 30 2.92-3.08 (m, 3H), 2.60-2.92 (m, 2H), 2.38-2.58 (m, 3H), 2.27 (t, 1H, J = 11.3 Hz), 1.70-2.05 (m, 4H) ppm. MS (CI, NH₃): 475 (base, M+H).

EXAMPLE 190

4-((±)-*cis*-2-(2,4-dichlorophenyl)-4,5,7,8,10,10a-hexahydropyrido[4,3-*b*]pyrrolo[3,2,1-*hi*]indol-9(6a*H*)-yl)-1-(4-fluorophenyl)-1-butanone

5

The title compound (36 mg, 37%) was prepared by the method of Example 189 from (±)-*cis*-2-(2,4-dichlorophenyl)-4,5,6a,7,8,9,10,10a-octahydropyrido[4,3-*b*]pyrrolo[3,2,1-*hi*]indole (65.8 mg, 0.19 mmol), 4-chloro-4'-fluorobutyrophenone (50.0 mg, 0.25 mmol), KI (31.5 mg, 0.19 mmol), and K₂CO₃ (50.0 mg, 0.57 mmol) after chromatographic purification as a white amorphous solid. ¹H NMR (CDCl₃, 300 MHz) δ 7.90-7.95 (m, 2 H), 7.37 (s, 1H), 7.16 (s, 2H), 7.03 (t, 2H, J = 8.8 Hz), 6.91 (s, 1H), 6.85 (s, 1H), 3.49 (bt, 1H, J = 8.0 Hz), 3.25-3.45 (m, 2H), 3.02-3.22 (m, 2H), 2.90-3.02 (m, 3H), 2.50-2.88 (m, 2H), 2.10-2.45 (m, 4H), 1.70-2.00 (m, 4H) ppm. MS (CI, NH₃): 509 (base, M+H).

15

EXAMPLE 191

4-((±)-*cis*-5,6,8,9,11,11a-hexahydro-4*H*-pyrido[3',4':4,5]pyrrolo[3,2,1-*ij*]qionolin-10(7a*H*)-yl)-1-(4-fluorophenyl)-1-butanone

The title compound (19.1 mg, 56%) was prepared by the method of Example 189 from (±)-*cis*-5,6,7a,8,9,10,11,11a-octahydro-4*H*-pyrido[3',4':4,5]pyrrolo[3,2,1-*ij*]qionoline (30.0 mg, 0.09 mmol), 4-chloro-4'-fluorobutyrophenone (23.0 mg, 0.12 mmol), KI (15.0 mg, 0.09 mmol), and K₂CO₃ (37.0 mg, 0.27 mmol) after chromatographic purification as a white amorphous solid. ¹H NMR (CDCl₃, 300 MHz) δ 7.91-7.96 (m, 2 H), 7.01-7.19 (m, 2H), 6.82 (d, 1H, J = 12.1 Hz), 6.80 (d, 1H, J = 11.7 Hz), 2.98-3.25 (m, 3H), 2.94 (t, 2H, J = 6.9 Hz), 2.80-2.85 (m, 1H), 2.55-2.75 (m, 3H), 2.20-2.55 (m, 4H), 1.80-2.18 (m, 7H) ppm. MS (ESI): 379 (base, M+H).

30

EXAMPLE 265

4-((±)-*cis*-4,5,7,8,10,10a-hexahydropyrido[4.3-*b*]pyrrolo[3,2,1-*hi*]indol-9(6a*H*)-yl)-1-(4-fluorophenyl)-1-butanone

A mixture of (±)-*cis*-4,5,6a,7,8,9,10,10a-octahydropyrido[4.3-*b*]pyrrolo[3,2,1-*hi*] indole (2.8 g, 14 mmol), 4-chloro-4'-fluorobutyrophenone (4.21 g, 21 mmol), triethylamine (3 mL), KI (3.48 g, 21 mmol), dioxane (25 mL), and toluene (25 mL) was stirred and refluxed for 15 h under an atmosphere of nitrogen and then evaporated under reduced pressure to remove the volatiles. The residue was triturated with a small volume of dichloromethane and decanted from the insoluble material. The process was repeated two more times and the combined dichloromethane solution was added to 0.5N solution of hydrogen chloride in ether(200 mL). The salt that separated was filtered off, washed with ether, dissolved immediately in a minimum quantity of water and the solution extracted with ether. The ether extract was discarded and aqueous layer basified with 10% aqueous sodium hydroxide. The resulting mixture was extracted with dichloro- methane (2X) and the extract dried over magnesium sulfate and stripped of the solvent under reduced pressure to yield the title compound (3.3 g, 65%) as a highly viscous light brown liquid. ¹H NMR (CDCl₃, 300 MHz) δ 1.70-1.80 (m, 2H), 1.80-2.02 (m, 2H), 2.19 (t, J = 10.9 Hz, 1H), 2.30-2.52 (m, 3H), 2.62-2.72 (m, 1H), 2.72-2.85 (m, 1H), 2.99 (t, J = 7.0 Hz, 2H), 3.02-3.20 (m, 2H), 3.25-3.42 (m, 2H), 3.59-3.65 (m, 1H), 6.85 (s, 1H), 6.90 (s, 1H), 7.01 (t, J = 7.0 Hz, 2H), 7.98-8.03 (m, 2H) ppm. MS (CI): 365 (M+H⁺).

EXAMPLE 274

(6a*S*,10a*R*)-2-(2-fluoro-4-methoxyphenyl)-4,5,6a,7,8,9,10,10a-octahydropyrido[4,3-*b*]pyrrolo[3,2,1-*hi*]indole

Step A:

Tert-butyl (6a*S*,10a*R*)-2-(2-fluoro-4-methoxyphenyl)-4,5,7,8,10,10a-hexahydropyrido[4,3-*b*]pyrrolo[3,2,1-*hi*]indole-9(6a*H*)-carboxylate (116mg, 55%) was prepared by the method of Example 89 step C from *tert*-butyl (6a*S*,10a*R*)-2-bromo-4,5,7,8,10,10a-hexahydropyrido[4,3-*b*]pyrrolo[3,2,1-*hi*]indole-9(6a*H*)-

carboxylate (189mg, 0.5 mmol) and 2-fluoro-4-methoxyphenylboronic acid (158mg, 1.0 mmol).

Step B:

5 The title compound was prepared by the method of Example 98 from *tert*-butyl (6a*S*,10a*R*)-2-(2-fluoro-4-methoxyphenyl)-4,5,7,8,10,10a-hexahydropyrido[4,3-*b*]pyrrolo[3,2,1-*hi*]indole-9(6a*H*)-carboxylate to afford the title compound (82mg, 93%). ¹H NMR (CDCl₃, 300 MHz) δ 7.24-7.30 (m, 1H), 7.08 (s, 1H), 7.02 (s, 1H), 6.65-6.73 (m, 2H), 3.81 (s, 3H), 3.66-3.71 (m, 1H), 3.32-3.49 (m, 3H), 3.01-3.30 (m, 10 4H), 2.82-2.97 (m, 2H), 2.25 (bs, 1H), 1.79-1.93 (m, 2H) ppm. MS – ESI: 325 [MH]⁺.

EXAMPLE 275

***tert*-butyl (6a*S*,10a*R*)-2-[4-ethoxy-2-(trifluoromethyl)phenyl]-4,5,7,8,10,10a-hexahydropyrido [4,3-*b*]pyrrolo[3,2,1-*hi*]indole-9(6a*H*)-carboxylate**

15 *Tert*-butyl (6a*S*,10a*R*)-2-bromo-4,5,7,8,10,10a-hexahydropyrido[4,3-*b*]pyrrolo[3,2,1-*hi*]indole-9(6a*H*) carboxylate (189mg, 0.5 mmol) was dissolved in DME (7.8 mL). Ba(OH)₂ 8H₂O (236.6mg, 0.75mmol) in H₂O (2.6 mL) was added. 4-ethoxy-2-trifluoromethylphenyl boronic acid (140mg, 0.6 mmol) was added followed
20 by Pd(PPh₃)₄ (12mg, 0.01 mmol). The reaction flask was degassed and refluxed under a nitrogen atmosphere for 18 hrs. After cooling to RT, the reaction was concentrated *in vacuo*. Water (10 mL) and EtOAc (10 mL) were added. The layers were separated and the aqueous phase was extracted with EtOAc (2 x 10 mL). The combined organic layer was washed with brine (2 x 10 mL), dried over MgSO₄ and
25 concentrated *in vacuo* and after chromatographic purification (30% EtOAc/Hexane) to afford the title compound (140mg, 57%). ¹H NMR (CDCl₃, 300 MHz) δ 7.20 (d, 2H, J = 5.9 Hz), 7.19 (s, 1H), 7.01 (dd, 1H, J = 6.2, 2.2 Hz), 6.85 (s, 1H), 6.81 (s, 1H), 4.05–4.10 (m, 3H), 3.82-3.94 (m, 1H), 3.64-3.68 (m, 1H), 3.22-3.44 (m, 4H), 2.84-3.10 (m, 3H), 1.80-1.90 (m, 2H), 1.42-1.47 (m, 12H) ppm. MS – ApCI: 489 [M+H⁺].

30

EXAMPLE 276

(6a*S*,10a*R*)-2-[4-ethoxy-2-(trifluoromethyl)phenyl]-4,5,6a,7,8,9,10,10a-octahydropyrido [4,3-*b*]pyrrolo[3,2,1-*hi*]indole

5 The title compound was prepared by the method of Example 98 from *tert*-butyl (6a*S*,10a*R*)-2-[4-ethoxy-2-(trifluoromethyl)phenyl]-4,5,7,8,10,10a-hexahydropyrido [4,3-*b*]pyrrolo[3,2,1-*hi*]indole-9(6a*H*)-carboxylate to afford the title compound (97mg, 87%). ¹H NMR (CDCl₃, 300 MHz) δ 7.17 (d, 1H, J = 8.1Hz), 7.12 (d, 1H, J = 2.9Hz), 6.93 (dd, 1H, J = 8.4, 2.6Hz), 6.77 (s, 1H), 6.71 (s, 1H), 4.00
10 (q, 2H, J = 6.9Hz), 3.61 (t, 1H, J = 8.0Hz), 2.93-3.41 (m, 6H), 2.75-2.86 (m, 3H), 1.62-1.97 (m, 3H), 1.37 (t, 3H, J = 6.9Hz) ppm. MS – ApCI: 389 [M+H⁺].

EXAMPLE 277

***tert*-butyl (6a*S*,10a*R*)-2-(4-chloro-2-fluorophenyl)-4,5,7,8,10,10a-hexahydropyrido[4,3-*b*]pyrrolo[3,2,1-*hi*]indole-9(6a*H*)-carboxylate**

15 The title compound was prepared by the method of Example 89 step C from *tert*-butyl (6a*S*,10a*R*)-2-bromo-4,5,7,8,10,10a-hexahydropyrido[4,3-*b*]pyrrolo[3,2,1-*hi*]indole-9(6a*H*) carboxylate (189mg, 0.5 mmol) and corresponding 4-chloro-2-fluorophenyl boronic acid (175mg, 1.0 mmol) to afford after chromatographic
20 purification the title compound (128mg, 60%). ¹H NMR (CDCl₃, 300 MHz) δ 7.28-7.29 (m,1H), 7.05-7.15 (m, 4H), 3.6-4.2 (m, 3H), 2.80-3.50 (m, 7H), 1.80-1.90 (m, 2H), 1.48 (s, 9H) ppm. MS – ApCI: 429 [M+H⁺].

25 EXAMPLE 278

(6a*S*,10a*R*)- 2-(4-chloro-2-fluorophenyl)-4,5,6a,7,8,9,10,10a-octahydropyrido [4,3-*b*]pyrrolo[3,2,1-*hi*]indole

30 The title compound was prepared by the method of Example 98 from *tert*-butyl (6a*S*,10a*R*)-2-(4-chloro-2-fluorophenyl)-4,5,7,8,10,10a-hexahydropyrido[4,3-*b*]pyrrolo[3,2,1-*hi*]indole-9(6a*H*)-carboxylate to afford the title compound (66mg,

67%). ¹H NMR (CDCl₃, 300 MHz) δ 7.29-7.35 (m, 1H), 6.99-7.15 (m, 4H), 3.60-3.80 (m, 1H), 2.80-3.50 (m, 9H), 1.70-1.95 (m, 2H), 1.62 (bs, 1H) ppm. MS – ApCI: 329 [M+H⁺].

5

EXAMPLE 279

***tert*-butyl (6a*S*,10a*R*)-2-[4-isopropoxy-2-(trifluoromethyl)phenyl]-4,5,7,8,10,10a-hexahydropyrido[4,3-*b*]pyrrolo[3,2,1-*hi*]indole-9(6a*H*)-carboxylate**

The title compound was prepared by the method of Example 89 step C from
 10 *tert*-butyl (6a*S*,10a*R*)-2-bromo-4,5,7,8,10,10a-hexahydropyrido[4,3-*b*]pyrrolo[3,2,1-*hi*]indole-9(6a*H*) carboxylate (189mg, 0.5 mmol) and 4-isopropoxy-2-(trifluoromethyl)phenylboronic acid (248mg, 1.0 mmol) to afford after chromatographic purification the title compound (186mg, 74%). ¹H NMR (CDCl₃, 300 MHz) δ 7.11-7.18 (m,2H), 6.90-6.94 (m, 1H), 6.78 (s, 1H), 6.74 (s, 1H), 4.50-
 15 4.54 (m, 1H), 3.75-3.85 (m, 1H), 3.59-3.70 (m, 1H), 2.79-3.40 (m, 8H), 1.74-1.84 (m, 2H), 1.40 (s, 9H), 1.21 (d, 6H, J = 5.9Hz) ppm. MS – ApCI: 503 [M+H⁺].

EXAMPLE 280

(6a*S*,10a*R*)-2-[4-isopropoxy-2-(trifluoromethyl)phenyl]-4,5,6a,7,8,9,10,10a-octahydropyrido [4,3-*b*]pyrrolo[3,2,1-*hi*]indole

The title compound was prepared by the method of Example 98 from *tert*-butyl (6a*S*,10a*R*)-2-[4-isopropoxy-2-(trifluoromethyl)phenyl]-4,5,7,8,10,10a-hexahydropyrido[4,3-*b*]pyrrolo[3,2,1-*hi*]indole-9(6a*H*)-carboxylate to afford the title
 25 compound (96mg, 65%). ¹H NMR (CDCl₃, 300 MHz) δ 7.14 (d, 1H, J = 8.4Hz), 7.10 (d, 1H, J = 2.5Hz), 6.90 (dd, 1H, J = 2.6, 8.4Hz), 6.75 (s, 1H), 6.69 (s, 1H), 4.46-4.54 (m, 1H), 3.56-3.62 (m, 1H), 2.91-3.39 (m, 6H), 2.73-2.83 (m, 3H), 1.64-1.82 (m, 3H), 1.46 (d, 6H, J = 5.8Hz) ppm. MS – ApCI: 403 [M+H⁺].

EXAMPLE 281

***tert*-butyl (6a*S*,10a*R*)-2-[4-methoxy-2-(trifluoromethyl)phenyl]-4,5,7,8,10,10a-hexahydropyrido[4,3-*b*]pyrrolo[3,2,1-*hi*]indole-9(6a*H*)-carboxylate**

5 The title compound was prepared by the method of Example 89 step C from *tert*-butyl (6a*S*,10a*R*)-2-bromo-4,5,7,8,10,10a-hexahydropyrido[4,3-*b*]pyrrolo[3,2,1-*hi*]indole-9(6a*H*) carboxylate (189mg, 0.5 mmol) and 4-methoxy-2-(trifluoromethyl)phenylboronic acid (248mg, 1.0 mmol) to afford after chromatographic purification the title compound (196mg, 83%). ¹H NMR (CDCl₃,
10 300 MHz) δ 7.21-7.26 (m,2H), 7.01-7.05 (m, 1H), 6.86 (s, 1H), 6.82 (s, 1H), 3.90-4.30 (m, 3H), 3.86 (s, 3H), 3.3.64-3.75 (m, 1H), 3.25-3.50 (m, 4H), 3.05-3.12 (m, 1H), 2.85-2.95 (m, 1H), 1.80-1.90 (m, 2H), 1.47 (s, 9H) ppm. MS – ApCI: 475 [M+H⁺].

15

EXAMPLE 282

(6a*S*,10a*R*)-2-[4-methoxy-2-(trifluoromethyl)phenyl]-4,5,6a,7,8,9,10,10a-octahydropyrido [4,3-*b*]pyrrolo[3,2,1-*hi*]indole

 The title compound was prepared by the method of Example 98 from *tert*-
20 butyl (6a*S*,10a*R*)-2-[4-methoxy-2-(trifluoromethyl)phenyl]-4,5,7,8,10,10a-hexahydropyrido[4,3-*b*]pyrrolo[3,2,1-*hi*]indole-9(6a*H*)-carboxylate to afford the title compound (94mg, 61%). ¹H NMR (CDCl₃, 300 MHz) δ 7.20-7.25 (m, 2H), 7.02 (dd, 1H, J = 8.6, 2.5Hz), 6.85 (s, 1H), 6.77 (m, 1H), 3.86 (s, 1H), 3.64-3.74 (m, 1H), 3.26-3.48 (m, 3H), 3.02-3.24 (m, 3H), 2.82-2.98 (m, 3H), 1.74-1.96 (m, 3H) ppm. MS
25 – ApCI: 375 [M+H⁺].

EXAMPLE 283

***tert*-butyl (6a*S*,10a*R*)-2-phenyl-4,5,7,8,10,10a-hexahydropyrido[4,3-*b*]pyrrolo[3,2,1-*hi*]indole-9(6a*H*)-carboxylate**

5 The title compound was prepared by the method of Example 89 step C from *tert*-butyl (6a*S*,10a*R*)-2-bromo-4,5,7,8,10,10a-hexahydropyrido[4,3-*b*]pyrrolo[3,2,1-*hi*]indole-9(6a*H*) carboxylate (189mg, 0.5 mmol) and phenylboronic acid (122mg, 1.0 mmol) to afford after chromatographic purification the title compound (74mg, 20%).
¹H NMR (CDCl₃, 300 MHz) δ 7.49 (d, 2H, J = 7.7Hz), 7.34-7.40 (m, 2H), 7.25-7.30
 10 (m, 1H), 7.20 (s, 1H), 7.15 (s, 1H), 3.85-3.95 (m, 1H), 3.68-3.70 (m, 1H), 3.24-3.52 (m, 4H), 2.84-3.22 (m, 4H), 1.82-1.94 (m, 2H), 1.49 (s, 9H) ppm. MS – ApCI: 377 [M+H⁺].

EXAMPLE 284

(6a*S*,10a*R*)-2-phenyl-4,5,6a,7,8,9,10,10a-octahydropyrido [4,3-*b*]pyrrolo[3,2,1-*hi*]indole

 The title compound was prepared by the method of Example 98 from *tert*-butyl (6a*S*,10a*R*)-2-phenyl-4,5,7,8,10,10a-hexahydropyrido[4,3-*b*]pyrrolo[3,2,1-*hi*]indole-9(6a*H*)-carboxylate to afford the title compound (35mg, 64%).
 20 ¹H NMR (CDCl₃, 300 MHz) δ 7.49 (d, 2H, J = 7.7 Hz), 7.34-7.40 (m, 2H), 7.22-7.27 (m, 1H), 7.19 (s, 1H), 7.13 (s, 1H), 3.68-3.73 (m, 1H), 2.98-3.56 (m, 6H), 2.82-2.96 (m, 3H), 1.70-1.96 (m, 2H), 1.63 (bs, 1H) ppm. MS – ApCI: 277 [M+H⁺].

EXAMPLE 285

***tert*-butyl (6a*S*,10a*R*)-2-(2-methylphenyl)-4,5,7,8,10,10a-hexahydropyrido[4,3-*b*]pyrrolo[3,2,1-*hi*]indole-9(6a*H*)-carboxylate**

 The title compound was prepared by the method of Example 89 step C from
 30 *tert*-butyl (6a*S*,10a*R*)-2-bromo-4,5,7,8,10,10a-hexahydropyrido[4,3-*b*]pyrrolo[3,2,1-*hi*]indole-9(6a*H*) carboxylate (189mg, 0.5 mmol) and 2-methylphenylboronic acid

(136mg, 1.0 mmol) to afford after chromatographic purification the title compound (90mg, 46%). ¹H NMR (CDCl₃, 300 MHz) δ 7.11-7.18 (m, 4H), 6.82 (s, 1H), 6.77 (s, 1H), 3.86-4.30 (m, 2H), 3.58-3.64 (m, 1H), 2.76-3.42 (m, 7H), 2.20 (s, 3H), 1.70-1.85 (m, 2H), 1.40 (s, 9H) ppm. MS – ApCI: 391 [M+H⁺].

5

EXAMPLE 286**(6a*S*,10a*R*)-2-(2-methylphenyl)-4,5,6a,7,8,9,10,10a-octahydropyrido [4,3-*b*]pyrrolo[3,2,1-*hi*]indole**

10 The title compound was prepared by the method of Example 98 from *tert*-butyl (6a*S*,10a*R*)-2-(2-methylphenyl)-4,5,7,8,10,10a-hexahydropyrido[4,3-*b*]pyrrolo[3,2,1-*hi*]indole-9(6a*H*)-carboxylate to afford the title compound (52mg, 78%). ¹H NMR (CDCl₃, 300 MHz) δ 7.09-7.18 (m, 4H), 6.80 (s, 1H), 6.74 (s, 1H), 3.59-3.65 (m, 1H), 2.93-3.42 (m, 6H), 2.74-2.87 (m, 3H), 2.20 (s, 3H), 1.66-1.85 (m, 2H), 1.51 (bs, 1H) ppm. MS – ApCI: 291 [M+H⁺].

15

EXAMPLE 287***tert*-butyl (6a*S*,10a*R*)-2-[2-(trifluoromethyl)phenyl]-4,5,7,8,10,10a-hexahydropyrido[4,3-*b*]pyrrolo[3,2,1-*hi*]indole-9(6a*H*)-carboxylate**

20

The title compound was prepared by the method of Example 89 step C from *tert*-butyl (6a*S*,10a*R*)-2-bromo-4,5,7,8,10,10a-hexahydropyrido[4,3-*b*]pyrrolo[3,2,1-*hi*]indole-9(6a*H*) carboxylate (189mg, 0.5 mmol) and 2-(trifluoromethyl)phenylboronic acid (190mg, 1.0 mmol) to afford after

25 chromatographic purification the title compound (175mg, 79%). ¹H NMR (CDCl₃, 300 MHz) δ 7.69 (d, 1H, J = 7.7Hz), 7.50 (dd, 1H, J = 7.3, 7.7Hz), 7.40 (dd, 1H, J = 7.7, 7.3Hz), 7.31 (d, 1H, J = 7.3Hz), 6.89 (s, 1H), 6.85 (s, 1H), 3.82-4.30 (m, 2H), 3.66-3.71 (m, 1H), 2.88-3.50 (m, 7H), 1.80-1.90 (m, 2H), 1.47 (s, 9H) ppm. MS – ApCI: 445 [M+H⁺].

30

EXAMPLE 288

**(6a*S*,10a*R*)-2-[2-(trifluoromethyl)phenyl]-4,5,6a,7,8,9,10,10a-octahydropyrido
[4,3-*b*]pyrrolo[3,2,1-*hi*]indole**

5 The title compound was prepared by the method of Example 98 from *tert*-butyl (6a*S*,10a*R*)-2-[2-(trifluoromethyl)phenyl]-4,5,7,8,10,10a-hexahydropyrido[4,3-*b*]pyrrolo[3,2,1-*hi*]indole-9(6a*H*)-carboxylate to afford the title compound (92mg, 68%). ¹H NMR (CDCl₃, 300 MHz) δ 7.71 (d, 1H, J = 7.6Hz), 7.51 (dd, 1H, J = 6.9, 7.4Hz), 7.33-7.42 (m, 2H), 6.89 (s, 1H), 6.83 (s, 1H), 3.68-3.73 (m, 1H), 3.03-3.48
10 (m, 7H), 2.83-2.99 (m, 3H), 1.74-1.94 (m, 2H), 1.59 (bs, 1H) ppm. MS – ApCI: 345 [M+H⁺].

EXAMPLE 289

***tert*-butyl (6a*S*,10a*R*)-2-(3,4-dimethoxyphenyl)-4,5,7,8,10,10a-
15 hexahydropyrido[4,3-*b*]pyrrolo[3,2,1-*hi*]indole-9(6a*H*)-carboxylate**

 The title compound was prepared by the method of Example 89 step C from *tert*-butyl (6a*S*,10a*R*)-2-bromo-4,5,7,8,10,10a-hexahydropyrido[4,3-*b*]pyrrolo[3,2,1-*hi*]indole-9(6a*H*) carboxylate (189mg, 0.5 mmol) and corresponding 3,4-
20 dimethoxyphenyl boronic acid (182mg, 1.0 mmol) to afford after chromatographic purification the title compound (92mg, 42%). ¹H NMR (CDCl₃, 300 MHz) δ 7.15 (s, 1H), 7.11 (s, 1H), 7.01-7.04 (m, 2H), 6.89 (d, 1H, J = 8.0Hz), 4.02-4.10 (m, 1H), 3.92 (d, 6H, J = 8.1Hz), 3.64-3.78 (m, 1H), 2.82-3.52 (m, 8H), 1.82-1.90 (m, 2H), 1.49 (s, 9H) ppm. MS – ApCI: 437 [M+H⁺].

25

EXAMPLE 290

**(6a*S*,10a*R*)-2-(3,4-dimethoxyphenyl)-4,5,6a,7,8,9,10,10a-octahydropyrido [4,3-
b]pyrrolo[3,2,1-*hi*]indole**

30 The title compound was prepared by the method of Example 98 from *tert*-butyl (6a*S*,10a*R*)-2-(3,4-dimethoxyphenyl)-4,5,7,8,10,10a-hexahydropyrido[4,3-

b]pyrrolo[3,2,1-*hi*]indole-9(6*aH*)-carboxylate to afford the title compound (52mg, 73%). ¹H NMR (CDCl₃, 300 MHz) δ 7.16 (s, 1H), 7.10 (s, 1H), 7.03-7.06 (m, 2H), 6.91(d, 1H, J = 8.8Hz), 3.93 (d, 6H, J = 8.1Hz), 3.69-3.75 (m, 1H), 2.83-3.52 (m, 9H), 1.74-1.94 (m, 3H) ppm. MS – ApCI: 337 [M+H⁺].

5

EXAMPLE 291

***tert*-butyl (6*aS*,10*aR*)-2-(2,5-dichlorophenyl)-4,5,7,8,10,10*a*-hexahydropyrido[4,3-*b*]pyrrolo[3,2,1-*hi*]indole-9(6*aH*)-carboxylate**

10 The title compound was prepared by the method of Example 89 step C from *tert*-butyl (6*aS*,10*aR*)-2-bromo-4,5,7,8,10,10*a*-hexahydropyrido[4,3-*b*]pyrrolo[3,2,1-*hi*]indole-9(6*aH*) carboxylate (189mg, 0.5 mmol) and 2,5-dichlorophenylboronic acid (191mg, 1.0 mmol) to afford after chromatographic purification the title compound (105mg, 47%). ¹H NMR (CDCl₃, 300 MHz) δ 7.30-7.36 (m, 2H), 7.15-7.19 (m, 1H),
15 7.01 (s, 1H), 3.82-4.22 (m, 2H), 3.82-3.96 (m, 1H), 2.82-3.52 (m, 7H), 1.82-1.90 (m, 2H), 1.48 (s, 9H) ppm. MS – ApCI: 445 [M+H⁺].

EXAMPLE 292

20 **(6*aS*,10*aR*)-2-(2,5-dichlorophenyl)-4,5,6*a*,7,8,9,10,10*a*-octahydropyrido [4,3-*b*]pyrrolo[3,2,1-*hi*]indole**

 The title compound was prepared by the method of Example 98 from *tert*-butyl (6*aS*,10*aR*)-2-(2,5-dichlorophenyl)-4,5,7,8,10,10*a*-hexahydropyrido[4,3-*b*]pyrrolo[3,2,1-*hi*]indole-9(6*aH*)-carboxylate to afford the title compound (60mg,
25 74%). ¹H NMR (CDCl₃, 300 MHz) δ 7.18-7.28 (m, 2H), 7.08 (dd, 1H, J = 2.6, 8.4Hz), 6.92 (s, 1H), 6.86 (s, 1H), 3.59-3.64 (m, 1H), 3.06-3.41 (m, 6H), 2.74-3.01 (m, 3H), 1.64-1.83 (m, 2H), 1.48 (bs, 1H) ppm. MS – ApCI: 345 [M+H⁺].

EXAMPLE 293

***tert*-butyl (6a*S*,10a*R*)-2-(3,5-dichlorophenyl)-4,5,7,8,10,10a-hexahydropyrido[4,3-*b*]pyrrolo[3,2,1-*hi*]indole-9(6a*H*)-carboxylate**

5 The title compound was prepared by the method of Example 89 step C from *tert*-butyl (6a*S*,10a*R*)-2-bromo-4,5,7,8,10,10a-hexahydropyrido[4,3-*b*]pyrrolo[3,2,1-*hi*]indole-9(6a*H*) carboxylate (189mg, 0.5 mmol) and 3,5-dichlorophenylboronic acid (191mg, 1.0 mmol) to afford after chromatographic purification the title compound (85mg, 38%). ¹H NMR (CDCl₃, 300 MHz) δ 7.35 (s, 2H), 7.21-7.23 (m, 1H), 7.13
10 (s, 1H), 7.10 (s, 1H), 3.82-4.22 (m, 2H), 3.65-3.75 (m, 1H), 2.84-3.52 (m, 7H), 1.80-1.90 (m, 2H), 1.49 (s, 9H) ppm. MS – ApCI: 445 [M+H⁺].

EXAMPLE 294

(6a*S*,10a*R*)-2-(3,5-dichlorophenyl)-4,5,6a,7,8,9,10,10a-octahydropyrido [4,3-*b*]pyrrolo[3,2,1-*hi*]indole

15

The title compound was prepared by the method of Example 98 from *tert*-butyl (6a*S*,10a*R*)-2-(3,5-dichlorophenyl)-4,5,7,8,10,10a-hexahydropyrido[4,3-*b*]pyrrolo[3,2,1-*hi*]indole-9(6a*H*)-carboxylate to afford the title compound (60mg, 74%). ¹H NMR (CDCl₃, 300 MHz) δ 7.27 (d, 2H, J = 1.9Hz), 7.12-7.14 (m, 1H),
20 7.05 (s, 1H), 6.99 (s, 1H), 3.59-3.65 (m, 1H), 3.00-3.41 (m, 5H), 2.91-2.99 (m, 1H), 2.74-2.89 (m, 3H), 1.65-1.83 (m, 2H), 1.49 (bs, 1H) ppm. MS – ApCI: 345 [M+H⁺].

EXAMPLE 295

***tert*-butyl (6a*S*,10a*R*)-2-(2-isopropyl-4-methoxyphenyl)-4,5,7,8,10,10a-hexahydropyrido[4,3-*b*]pyrrolo[3,2,1-*hi*]indole-9(6a*H*)-carboxylate**

25

The title compound was prepared by the method of Example 89 step C from *tert*-butyl (6a*S*,10a*R*)-2-bromo-4,5,7,8,10,10a-hexahydropyrido[4,3-*b*]pyrrolo[3,2,1-*hi*]indole-9(6a*H*) carboxylate (189mg, 0.5 mmol) and corresponding 2-isopropyl-4-methoxyphenyl boronic acid (178mg, 1.0 mmol) to afford after chromatographic

30

purification the title compound (152mg, 68%). ¹H NMR (CDCl₃, 300 MHz) δ 7.09 (d, 1H, J = 8.4Hz), 6.88 (d, 1H, J = 2.5 Hz), 6.83 (s, 1H), 6.78 (s, 1H), 6.72 (dd, 1H, J = 8.4, 2.9Hz), 3.80-4.20 (m, 2H), 3.84 (s, 3H), 3.74-3.78 (m, 1H), 3.05-3.50 (m, 7H), 2.84-2.98 (m, 1H), 1.82-1.94 (m, 2H), 1.48 (s, 9H), 1.12-1.17 (m, 6H) ppm. MS –

5 ApCI: 449. [M+H⁺].

EXAMPLE 296

(6a*S*,10a*R*)-2-(2-isopropyl-4-methoxyphenyl)-4,5,6a,7,8,9,10,10a-octahydropyrido [4,3-*b*]pyrrolo[3,2,1-*hi*]indole

10

The title compound was prepared by the method of Example 98 from *tert*-butyl (6a*S*,10a*R*)-2-(2-isopropyl-4-methoxyphenyl)-4,5,7,8,10,10a-hexahydropyrido[4,3-*b*]pyrrolo[3,2,1-*hi*]indole-9(6a*H*)-carboxylate to afford the title compound (88mg, 75%). ¹H NMR (CDCl₃, 300 MHz) δ 7.10 (d, 1H, J = 8.0Hz), 6.87 (d, 1H, J = 3.0Hz), 6.81 (s, 1H), 6.70-6.75 (m, 2H), 3.84 (s, 3H), 3.67-3.73 (m, 1H), 3.01-3.50 (m, 7H), 2.82-2.94 (m, 3H), 1.73-1.93 (m, 2H), 1.67 (bs, 1H), 1.14 (m, 6H) ppm. MS – ApCI: 349 [M+H⁺].

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EXAMPLE 297

***tert*-butyl (6a*S*,10a*R*)-2-(5-fluoro-4-methoxy-2-methylphenyl)-4,5,7,8,10,10a-hexahydropyrido[4,3-*b*]pyrrolo[3,2,1-*hi*]indole-9(6a*H*)-carboxylate**

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The title compound was prepared by the method of Example 89 step C from *tert*-butyl (6a*S*,10a*R*)-2-bromo-4,5,7,8,10,10a-hexahydropyrido[4,3-*b*]pyrrolo[3,2,1-*hi*]indole-9(6a*H*) carboxylate (189mg, 0.5 mmol) and corresponding 5-fluoro-4-methoxy-2-methylphenyl boronic acid (184mg, 1.0 mmol) to afford after chromatographic purification the title compound (130mg, 60%). ¹H NMR (CDCl₃, 300 MHz) δ 6.94 (d, 1H, J = 12.5Hz), 6.84 (s, 1H), 6.79-6.82 (m, 2H), 4.02-4.22 (m, 1H), 3.90 (s, 3H), 3.82-3.92 (m, 1H), 3.64-3.74 (m, 1H), 3.24-3.54 (m, 4H), 2.86-3.22 (m, 3H), 2.22 (s, 3H), 1.82-1.94 (m, 2H), 1.48 (s, 9H) ppm. MS – ApCI: 439 [M+H⁺].

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EXAMPLE 298

(6a*S*,10a*R*)-2-(5-fluoro-4-methoxy-2-methylphenyl)-4,5,6a,7,8,9,10,10a-octahydropyrido [4,3-*b*]pyrrolo[3,2,1-*hi*]indole

5

The title compound was prepared by the method of Example 98 from *tert*-butyl (6a*S*,10a*R*)-2-(5-fluoro-4-methoxy-2-methylphenyl)-4,5,7,8,10,10a-hexahydropyrido[4,3-*b*]pyrrolo[3,2,1-*hi*]indole-9(6a*H*)-carboxylate to afford the title compound (85mg, 85%). ¹H NMR (CDCl₃, 300 MHz) δ 6.93 (d, 1H, J = 13.1Hz), 6.77-6.82 (m, 3H), 3.90 (s, 3H), 3.66-3.72 (m, 1H), 3.01-3.49 (m, 6H), 2.81-2.94 (m, 3H), 2.23 (s, 3H), 1.69-1.93 (m, 3H) ppm. MS – ApCI: 339 [M+H⁺].

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EXAMPLE 299

***tert*-butyl (6a*S*,10a*R*)-2-(4-methoxy-2-methylphenyl)-4,5,7,8,10,10a-hexahydropyrido[4,3-*b*]pyrrolo[3,2,1-*hi*]indole-9(6a*H*)-carboxylate**

15

The title compound was prepared by the method of Example 89 step C from *tert*-butyl (6a*S*,10a*R*)-2-bromo-4,5,7,8,10,10a-hexahydropyrido[4,3-*b*]pyrrolo[3,2,1-*hi*]indole-9(6a*H*) carboxylate (189mg, 0.5 mmol) and 4-methoxy-2-methylphenylboronic acid (166mg, 1.0 mmol) to afford after chromatographic purification the title compound (105mg, 50%). ¹H NMR (CDCl₃, 300 MHz) δ 7.04 (d, 1H, J = 8.5Hz), 6.65-6.79 (m, 4H), 3.75-4.22 (m, 2H), 3.74 (s, 3H), 3.58-3.68 (m, 1H), 3.18-3.42 (m, 4H), 2.76-3.16 (m, 3H), 2.17 (s, 3H), 1.70-1.84 (m, 2H), 1.40 (s, 9H) ppm. MS – ApCI: 421 [M+H⁺].

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EXAMPLE 300

(6a*S*,10a*R*)-2-(4-methoxy-2-methylphenyl)-4,5,6a,7,8,9,10,10a-octahydropyrido [4,3-*b*]pyrrolo[3,2,1-*hi*]indole

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The title compound was prepared by the method of Example 98 from *tert*-butyl (6a*S*,10a*R*)-2-(4-methoxy-2-methylphenyl)-4,5,7,8,10,10a-hexahydropyrido[4,3-

b]pyrrolo[3,2,1-*hi*]indole-9(6*aH*)-carboxylate to afford the title compound (50mg, 63%). ¹H NMR (CDCl₃, 300 MHz) δ 7.14 (d, 1H, J = 8.5Hz), 6.85 (s, 1H), 6.73-6.79 (m, 3H), 3.82 (s, 3H), 3.67-3.69 (m, 1H), 3.02-3.50 (m, 6H), 2.82-2.94 (m, 3H), 2.26 (s, 3H), 1.73-1.93 (m, 2H), 1.63 (bs, 1H) ppm. MS – ApCI: 321 [M+H⁺].

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EXAMPLE 301

***tert*-butyl (6*aS*,10*aR*)-2-(2-chloro-4-methoxyphenyl)-4,5,7,8,10,10*a*-hexahydropyrido[4,3-*b*]pyrrolo[3,2,1-*hi*]indole-9(6*aH*)-carboxylate**

10 The title compound was prepared by the method of Example 89 step C from *tert*-butyl (6*aS*,10*aR*)-2-bromo-4,5,7,8,10,10*a*-hexahydropyrido[4,3-*b*]pyrrolo[3,2,1-*hi*]indole-9(6*aH*) carboxylate (189mg, 0.5 mmol) and 2-chloro-4-methoxyphenylboronic acid (187mg, 1.0 mmol) to afford after chromatographic purification the title compound (133mg, 60%). ¹H NMR (CDCl₃, 300 MHz) δ 7.23
15 (d, 1H, J = 8.8Hz), 7.01 (s, 2H), 6.97 (s, 1H), 6.84 (dd, 1H, J = 8.5, 2.6Hz), 3.84-4.24 (m, 2H), 3.84 (s, 3H), 3.68-3.74 (m, 1H), 3.24-3.54 (m, 4H), 2.86-3.26 (m, 3H), 1.84-1.8 (m, 2H), 1.49 (s, 9H) ppm. MS – ApCI: 441 [M+H⁺].

EXAMPLE 302

20 **(6*aS*,10*aR*)-2-(2-chloro-4-methoxyphenyl)-4,5,6*a*,7,8,9,10,10*a*-octahydropyrido[4,3-*b*]pyrrolo[3,2,1-*hi*]indole**

The title compound was prepared by the method of Example 98 from *tert*-butyl (6*aS*,10*aR*)-2-(2-chloro-4-methoxyphenyl)-4,5,7,8,10,10*a*-hexahydropyrido[4,3-*b*]pyrrolo[3,2,1-*hi*]indole-9(6*aH*)-carboxylate to afford the title compound (66mg, 64%). ¹H NMR (CDCl₃, 300 MHz) δ 7.24 (d, 1H, J = 8.4Hz), 7.00-7.01 (m, 2H),
25 6.94 (s, 1H), 6.83 (dd, 1H, J = 8.7, 2.6Hz), 3.84 (s, 3H), 3.68-3.74 (m, 1H), 3.02-3.51 (m, 6H), 2.85-2.95 (m, 3H), 1.76-1.93 (m, 2H), 1.63 (bs, 1H) ppm. MS – ApCI: 341 [M+H⁺].

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EXAMPLE 303

***tert*-butyl (6a*S*,10a*R*)-2-(3-chloro-2-methylphenyl)-4,5,7,8,10,10a-hexahydropyrido[4,3-*b*]pyrrolo[3,2,1-*hi*]indole-9(6a*H*)-carboxylate**

The title compound was prepared by the method of Example 89 step C from *tert*-butyl (6a*S*,10a*R*)-2-bromo-4,5,7,8,10,10a-hexahydropyrido[4,3-*b*]pyrrolo[3,2,1-*hi*]indole-9(6a*H*) carboxylate (189mg, 0.5 mmol) and 3-chloro-2-methylphenylboronic acid (140mg, 1.0 mmol) to afford after chromatographic purification the title compound (99mg, 47%). ¹H NMR (CDCl₃, 300 MHz) δ 7.28-7.31 (m, 1H), 7.10 (d, 2H, J = 4.4Hz), 6.85 (s, 1H), 6.81 (s, 1H), 3.82-4.24 (m, 2H), 3.64-3.74 (m, 1H), 3.24-3.54 (m, 4H), 2.86-3.26 (m, 3H), 1.86 (s, 3H), 1.84-1.89 (m, 2H), 1.48 (s, 9H) ppm. MS – ApCI: 425 [M+H⁺].

EXAMPLE 304

(6a*S*,10a*R*)-2-(3-chloro-2-methylphenyl)-4,5,6a,7,8,9,10,10a-octahydropyrido[4,3-*b*]pyrrolo[3,2,1-*hi*]indole

The title compound was prepared by the method of Example 98 from *tert*-butyl (6a*S*,10a*R*)-2-(3-chloro-2-methylphenyl)-4,5,7,8,10,10a-hexahydropyrido[4,3-*b*]pyrrolo[3,2,1-*hi*]indole-9(6a*H*)-carboxylate to afford the title compound (48mg, 63%). ¹H NMR (CDCl₃, 300 MHz) δ 7.27-7.30 (m, 1H), 7.07-7.13 (m, 2H), 6.83 (s, 1H), 6.78 (s, 1H), 3.67-3.73 (m, 1H), 3.01-3.50 (m, 6H), 2.83-2.94 (m, 3H), 2.29 (s, 3H), 1.75-1.93 (m, 2H), 1.62 (bs, 1H) ppm. MS – ApCI: 325 [M+H⁺].

EXAMPLE 305

2-[(6a*S*,10a*R*)-4,5,6a,7,8,9,10,10a-octahydropyrido[4,3-*b*]pyrrolo[3,2,1-*hi*]-2-yl]-5-methoxybenzaldehyde

Step A:

To a solution of *tert*-butyl(6a*S*, 10a*R*)-2-bromo-4,5,7,8,10,10a-hexahydropyrido[4,3-*b*]pyrrolo[3,2,1-*hi*]indole-9(6a*H*)-carboxylate (0.600 g, 1.59 mmol) in DME (35 mL) was added 2-formyl-4-methoxybenzeneboronic acid (0.344

g, 1.91 mmol), tetrakis(triphenylphosphine)palladium(0) (0.110 g), barium hydroxide octahydrate (0.753 g, 2.39 mmol), and H₂O (10 mL). The combined mixture was refluxed for 20 h. Once at room temperature, the mixture was taken up in H₂O (300 mL) and extracted with EtOAc (3 x 100 mL). The combined extracts were dried over
 5 MgSO₄ and stripped of solvent under reduced pressure. Purification by normal phase HPLC using 25% EtOAc in hexanes afforded 0.280 g (41%) of *tert*-butyl (6a*S*,10a*R*)-2-(2-formyl-4-methoxyphenyl)-4,5,7,8,10,10a-hexahydropyrido[4,3-*b*]pyrrolo[3,2,1-*hi*]indole-9(6a*H*)-carboxylate.

10 Step B:

A solution of *tert*-butyl (6a*S*,10a*R*)-2-(2-formyl-4-methoxyphenyl)-4,5,7,8,10,10a-hexahydropyrido[4,3-*b*]pyrrolo[3,2,1-*hi*]indole-9(6a*H*)-carboxylate (0.066 g, 0.15 mmol) in CH₂Cl₂ (5 mL) was treated with TFA (2 mL) and stirred at room temperature for 18 h in a closed vial. The solution was basified with 1N NaOH
 15 (50 mL) and extracted with CH₂Cl₂ (3 x 25 mL). The combined extracts were dried over Na₂SO₄, and stripped of the solvent under reduced pressure to yield 0.042 g (82%) of 2-[(6a*S*,10a*R*)-4,5,6a,7,8,9,10,10a-octahydropyrido[4,3-*b*]pyrrolo[3,2,1-*hi*]-2-yl]-5-methoxybenzaldehyde as a foam. ¹H NMR (CDCl₃, 300 MHz) δ 7.45 (d, 1H), 7.35 (d, 1H), 7.16 (dd, 1H), 6.92 (d, 1H), 6.86 (d, 1H), 3.88 (s, 1H), 3.74 (td,
 20 1H), 3.51-3.24 (m, 3H), 3.23-3.00 (m, 2H), 2.98-2.83 (m, 1H), 2.00-1.92 (m, 2H). MS (CI): 337 (M+H⁺).

EXAMPLE 306

(6a*S*,10a*R*)-2-(2,6-dichlorophenyl)-4,5,6a,7,8,9,10,10a-octahydropyrido[4,3-*b*]pyrrolo[3,2,1-*hi*]indole
 25

The title compound was prepared by Example 305, Step A, from *tert*-butyl(6a*S*, 10a*R*)-2-bromo-4,5,7,8,10,10a-hexahydropyrido[4,3-*b*]pyrrolo[3,2,1-*hi*]indole-9(6a*H*)-carboxylate and the corresponding 2,6-dichlorobenzeneboronic acid
 30 followed by hydrolysis of the resultant BOC protected amine adduct by the procedure of Example 305, Step B. ¹H NMR (CDCl₃, 300 MHz) δ 7.38 (dd, 2H), 7.15 (t, 1H),

6.80 (d, 1H), 6.73 (d, 1H), 3.69 (td, 1H), 3.57-3.30(m, 3H), 3.28-3.00 (m, 3H), 3.00-2.83 (m, 3H), 2.20 (bs, 2H), 2.00-1.81 (m, 2H). MS (CI): 346 (M+H⁺).

EXAMPLE 307

5 ***N*-[4-[(6a*S*,10a*R*)-4,5,6a,7,8,9,10,10a-octahydropyrido[4,3-*b*]pyrrolo[3,2,1-*hi*]indol-2-yl]-3-(trifluoromethyl)phenyl]-*N*-methylamine**

The title compound was prepared by Example 305, Step A, from *tert*-butyl(6a*S*, 10a*R*)-2-bromo-4,5,7,8,10,10a-hexahydropyrido[4,3-*b*]pyrrolo[3,2,1-*hi*]indole-9(6a*H*)-carboxylate and the corresponding 2-
10 (trifluoromethyl)benzeneboronic acid followed by hydrolysis of the resultant BOC protected amine adduct by the procedure of Example 305, Step B. ¹H NMR (CDCl₃, 300 MHz) δ 7.09 (d, 1H), 6.76 (dd, 2H), 6.70 (dd, 1H), 6.63 (dd, 2H), 3.80 (bs, 1H), 3.60 (t, 1H), 3.41-2.96 (m, 5H), 2.95-2.73 (m, 4H), 2.10 (bs, 2H), 1.98-1.75 (m, 2H).
15 MS (CI): 374 (M+H⁺).

EXAMPLE 308

4-[(6a*S*,10a*R*)-4,5,6a,7,8,9,10,10a-octahydropyrido[4,3-*b*]pyrrolo[3,2,1-*hi*]indol-2-yl]-3-(trifluoromethyl)phenylamine

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The title compound was prepared by Example 305, Step A, from *tert*-butyl(6a*S*,10a*R*)-2-bromo-4,5,7,8,10,10a-hexahydropyrido[4,3-*b*]pyrrolo[3,2,1-*hi*]indole-9(6a*H*)-carboxylate and the corresponding 2-
(trifluoromethyl)benzeneboronic acid followed by hydrolysis of the resultant BOC
25 protected amine adduct by the procedure of Example 305, Step B. ¹H NMR (CDCl₃, 300 MHz) δ 7.03 (d, 1H), 6.90 (d, 1H), 6.79-6.70 (m, 3H), 3.78 (bs, 1H), 3.60 (t, 1H), 3.41-3.18 (m, 2H), 3.17-2.79 (m, 5H), 2.27 (bs, 2H), 1.90-1.80 (m, 2H). MS (CI): 360 (M+H⁺).

EXAMPLE 309

1-(2-[(6a*S*,10a*R*)-4,5,6a,7,8,9,10,10a-octahydropyrido[4,3-*b*]pyrrolo[3,2,1-*hi*]indol-2-yl]-5-methoxyphenyl)ethanol

5 To a solution of 2-[(6a*S*,10a*R*)-4,5,6a,7,8,9,10,10a-octahydropyrido[4,3-*b*]pyrrolo[3,2,1-*hi*]-2-yl]-5-methoxybenzaldehyde (0.156 g, 0.47 mmol) from Example 305 in freshly distilled THF (8 mL) at -78°C was added 3.0 M methylmagnesiumbromide in diethylether (0.88 mL, 2.65 mmol). The reaction was stirred at room temperature for 18 h under a nitrogen atmosphere. The reaction

10 mixture was quenched with aqueous ammonium chloride (20 mL) and extracted with EtOAc (3 x 10 mL). The combined extracts were dried over Na₂SO₄ and evaporated to dryness under reduced pressure to yield a 60% mixture of product and 40% starting material. Purification by reverse phase HPLC using a gradient of 0-100% water, acetonitrile with 0.1% TFA afforded 0.024 g (15%) of 1-(2-[(6a*S*,10a*R*)-

15 4,5,6a,7,8,9,10,10a-octahydropyrido[4,3-*b*]pyrrolo[3,2,1-*hi*]indol-2-yl]-5-methoxyphenyl)ethanol after generation of the free base. ¹H NMR (CDCl₃, 300 MHz) δ 7.18 (d, 1H), 7.13 (dd, 1H), 6.80 (dd, 2H), 6.77 (d, 1H), 5.03-4.96 (m, 1H), 3.85 (s, 3H), 3.68 (dt, 1H), 3.51-3.39 (m, 1H), 3.36-3.28 (m, 2H), 3.21-3.00 (m, 3H), 2.98-2.80 (m, 3H), 2.00-1.78 (m, 2H), 1.19 (q, 3H). MS (CI): 351 (M+H⁺).

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EXAMPLE 310

(±)-*cis*-4,5,6,7,8a,9,10,11,12,12a-decahydroazepino[3,2,1-*hi*]pyrido[4,3-*b*]indole

Step A:

25 Sodium azide (1.95 g, 30 mmol) was added in small portions to a solution of 3,4-dihydro-1(2*H*)-naphthalenone (2.92 g, 20 mmol) in CH₃SO₃H (50 mL) at 0°C. The mixture was stirred at 0°C for 15 min, 1hr at room temperature, poured into ice (400 mL), basified until pH > 8 with 1N NaOH at 0°C and extracted with ether (3 x 100 mL). The combined organic layer was dried (MgSO₄), concentrated *in vacuo* and

30 flash column chromatography (EtOAc:hexane / 1:1) gave 1,3,4,5-tetrahydro-2*H*-1-benzazepin-2-one (2.71 g, 85%) as a white solid. ¹H NMR (CDCl₃, 300 MHz) δ 2.18-

2.32 (m, 2H), 2.36 (t, $J = 7.1$ Hz, 2H), 2.80 (t, $J = 7.6$ Hz, 2H), 6.99 (d, $J = 8.1$ Hz, 1H), 7.13 (td, $J = 7.6, 1.5$ Hz, 1H), 7.22 (d, $J = 7.0$ Hz, 2H), 8.10 (br, 1H) ppm.

Step B:

5 A solution of 1,3,4,5-tetrahydro-2*H*-1-benzazepin-2-one (2.71 g, 16.7 mmol) in THF (40 mL) was added dropwise to a suspension of LAH (1.27 g, 33.4 mmol) in ether (150 mL) at room temperature. The mixture was refluxed for 16h. Saturated Rochelle's salt solution (15 mL) was added to the mixture cooled with an ice-water bath. The mixture was stirred for 2hrs and the two layers were separated. The
10 aqueous layer was extracted with ether (2×25 mL). The combined organic layer was dried (Na_2SO_4), concentrated *in vacuo* and flash column chromatography (EtOAc:hexane / 3:7) gave 2,3,4,5-tetrahydro-1*H*-1-benzazepine (2.40 g, 98%) as a yellow liquid. ^1H NMR (CDCl_3 , 300 MHz) δ 1.58-1.70 (m, 2H), 1.72-1.86 (m, 2H), 2.72-2.82 (m, 2H), 3.00-3.10 (m, 2H), 3.78 (br, 1H), 6.74 (dd, $J = 1.1, 7.7$ Hz, 1H),
15 6.82 (td, $J = 7.3, 1.1$ Hz, 1H), 7.04 (td, $J = 7.5, 1.5$ Hz, 1H), 7.11 (d, $J = 7.4$ Hz, 1H) ppm.

Step C:

20 A solution of sodium nitrite (1.35 g, 19.6 mmol) in water (4.0 mL) was added dropwise to a solution of 2,3,4,5-tetrahydro-1*H*-1-benzazepine (2.40 g, 16.3 mmol) in AcOH (10 mL) at 0-10°C. The mixture was stirred at 5°C for 10 min, room temperature for 1 h and extracted with CH_2Cl_2 (3×20 mL). The organic layer was dried (MgSO_4), concentrated *in vacuo* and flash column chromatography (EtOAc:hexane / 1:9) gave 1-nitroso-2,3,4,5-tetrahydro-1*H*-1-benzazepine (2.60 g,
25 91%) as a brown liquid. ^1H NMR (CDCl_3 , 300 MHz) δ 1.70-1.85 (m, 4H), 2.70-2.82 (m, 2H), 3.92 (br, 2H), 7.25-7.32 (m, 1H), 7.32-7.40 (m, 2H), 7.40-7.48 (m, 1H) ppm.

Step D:

30 A solution of 1-nitroso-2,3,4,5-tetrahydro-1*H*-1-benzazepine (2.60 g, 14.7 mmol) in THF (40 mL) was added dropwise under N_2 to a suspension of LAH (0.56 g, 14.7 mmol) in THF (10 mL) cooled with an ice-bath such that the temperature did

not rise above 15°C. The mixture was stirred at room temperature for 1 h, quenched with saturated Rochelle's salt solution (15 mL) and extracted with ether (3 × 20 mL). The organic layer was dried (Na₂SO₄), concentrated *in vacuo* and flash column chromatography (EtOAc:hexane / 1:4) gave 2,3,4,5-tetrahydro-1*H*-1-benzazepin-amine (1.63 g, 68%) as a light yellow solid. ¹H NMR (CDCl₃, 300 MHz) δ 1.50-1.72 (m, 2H), 1.78-1.92 (m, 2H), 2.70-2.82 (m, 2H), 3.180-3.22 (m, 2H), 3.78 (br, 2H), 6.91 (td, J = 7.3, 1.5 Hz, 1H), 7.10 (dd, J = 1.1, 7.4 Hz, 1H), 7.21 (td, J=8.0, 1.4 Hz, 1H), 7.28 (dd, J = 1.4, 8.0 Hz, 1H) ppm.

10 Step E:

A mixture of 4-piperidone monohydrate HCl (1.54 g, 10 mmol) and 2,3,4,5-tetrahydro-1*H*-1-benzazepin-amine (1.62 g, 10 mmol) in IPA (50 mL) was refluxed for 2 h and cooled to room temperature. Concentrated HCl (0.82 mL, 10 mmol) was added and the resultant mixture was refluxed for 3 hrs before being cooled to room temperature. The solid was filtered, rinsed with cold IPA (2 × 20 mL) and concentrated *in vacuo*. 4,5,6,7,9,10,11,12-Octahydroazepino[3,2,1-*hi*]pyrido[4,3-*b*]indole hydrochloride (1.88 g, 71%) was obtained as a pink solid. 4,5,6,7,9,10,11,12-Octahydroazepino[3,2,1-*hi*]pyrido[4,3-*b*]indole hydrochloride (20 mg, 0.076 mmol) in water (1.0 mL) was basified with 1N NaOH until pH > 14 and extracted with CHCl₃ (3 × 10 mL). The combined organic layer was washed with brine (10 mL), dried (MgSO₄) and concentrated *in vacuo*. 4,5,6,7,9,10,11,12-Octahydroazepino[3,2,1-*hi*]pyrido[4,3-*b*]indole (16 mg, 95%) was obtained as a white foam. ¹H NMR (CDCl₃, 300 MHz) δ 1.83 (br, 1H), 2.00-2.20 (m, 4H), 2.72 (t, J = 5.7 Hz, 2H), 3.05-3.20 (m, 2H), 3.25 (t, J = 5.6 Hz, 2H), 3.92-4.02 (m, 2H), 4.05 (t, J = 1.6 Hz, 2H), 6.92 (d, J = 6.3 Hz, 1H), 6.98 (t, J = 7.4 Hz, 1H), 7.25 (dd, J = 1.0, 7.4 Hz, 1H) ppm.

Step F:

NaCNBH₃ (0.94 g, 15 mmol) was added in small portions to a solution of 4,5,6,7,9,10,11,12-octahydroazepino[3,2,1-*hi*]pyrido[4,3-*b*]indole hydrochloride (1.32 g, 5.0 mmol) in TFA (15 mL) at 0 °C. After stirring at room temperature for 2 h, the mixture was carefully treated with 6 N HCl (10 mL) and refluxed for 1 h. The mixture

was basified with 50% NaOH and extracted with CH₂Cl₂ (3 × 20 mL). The organic layer was dried (MgSO₄) and concentrated *in vacuo*. The title compound (1.0 g, 89%) was obtained as a yellow oil. ¹H NMR (CDCl₃, 300 MHz) δ 1.48-1.68 (m, 1H), 1.68-2.10 (m, 7H), 2.42-2.72 (m, 3H), 2.80-3.00 (m, 3H), 3.05 (dd, J = 6.3, 12.4 Hz, 1H),
5 3.12-3.55 (m, 2H), 6.69 (t, J = 7.4 Hz, 1H), 6.92 (dd, J = 2.5, 7.4 Hz, 2H) ppm.

EXAMPLE 311

***tert*-butyl (±)-*cis*-4,5,6,7,8a,9,10,11,12,12a-decahydroazepino[3,2,1-*hi*]pyrido[4,3-*b*]indole-11(8a*H*)-carboxylate**

10

1 N NaOH (10 mL) was added to a solution of (±)-*cis*-4,5,6,7,8a,9,10,11,12,12a-decahydroazepino[3,2,1-*hi*]pyrido[4,3-*b*]indole (1.00 g, 4.37 mmol) and di-*tert*-butyl dicarbonate (1.05 g, 4.8 mmol) in 1,4-dioxane (20 mL) and the mixture was stirred for 2 h at room temperature. The solvent was
15 concentrated *in vacuo* and EtOAc (30 mL) was added. The solution was washed with brine (30 mL), dried (MgSO₄), concentrated *in vacuo* and flash column chromatography (EtOAc:hexane / 1:4) gave the title compound (1.2 g, 83%) as a white solid.

20

EXAMPLE 312

(8a*S*,12a*R*)-4,5,6,7,8a,9,10,11,12,12a-decahydroazepino[3,2,1-*hi*]pyrido[4,3-*b*]indole

Step A:

25 *Tert*-Butyl (8a*S*,12a*R*)-4,5,6,7,9,10,12,12a-octahydroazepino[3,2,1-*hi*]pyrido[4,3-*b*]indole-11(8a*H*)-carboxylate was obtained from (±)-*tert*-butyl *cis*-4,5,6,7,9,10,12,12a-octahydroazepino[3,2,1-*hi*]pyrido[4,3-*b*]indole-11(8a*H*)-carboxylate by using preparative HPLC on a Chiracel[®] OD column (2% IPA in hexane).

30

Step B:

Tert-Butyl (8a*S*,12a*R*)-4,5,6,7,9,10,12,12a-octahydroazepino[3,2,1-*hi*]pyrido[4,3-*b*]indole-11(8a*H*)-carboxylate (0.24 g, 0.73 mmol) was stirred in 20% TFA in CH₂Cl₂ (10 mL) at room temperature for 2 h before the solution was basified with saturated NH₄OH until pH > 10. The layers were separated and the aqueous layer was extracted with CH₂Cl₂ (3 × 20 mL). The combined organic layer was washed with brine (20 mL), dried (MgSO₄) and concentrated *in vacuo*. The title compound (0.16 g, 94%) was obtained as a white foam. ¹H NMR was identical to (±)-*cis*-4,5,6,7,8a,9,10,11,12,12a-decahydroazepino[3,2,1-*hi*]pyrido[4,3-*b*]indole of Example 310.

EXAMPLE 313

(8a*R*,12a*S*)-4,5,6,7,8a,9,10,11,12,12a-decahydroazepino[3,2,1-*hi*]pyrido[4,3-*b*]indole

Step A:

Tert-butyl (8a*R*,12a*S*)-4,5,6,7,9,10,12,12a-octahydroazepino[3,2,1-*hi*]pyrido[4,3-*b*]indole-11(8a*H*)-carboxylate was obtained from (±)-*tert*-butyl *cis*-4,5,6,7,9,10,12,12a-octahydroazepino[3,2,1-*hi*]pyrido[4,3-*b*]indole-11(8a*H*)-carboxylate by using preparative HPLC on a Chiracel® OD column (2% IPA in hexane).

Step B:

The title compound (0.063 g, 98%) was prepared by the general method of Example 312, step B from *tert*-butyl (8a*R*,12a*S*)-4,5,6,7,9,10,12,12a-octahydroazepino[3,2,1-*hi*]pyrido[4,3-*b*]indole-11(8a*H*)-carboxylate (0.092 g, 0.28 mmol) as a white foam. ¹H NMR was identical to (±)-*cis*-4,5,6,7,8a,9,10,11,12,12a-decahydroazepino[3,2,1-*hi*]pyrido[4,3-*b*]indole of Example 310.

EXAMPLE 314

***tert*-butyl (8a*S*,12a*R*)-2-bromo-4,5,6,7,8a,9,10,11,12,12a-decahydroazepino[3,2,1-*hi*]pyrido[4,3-*b*]indole-11(8a*H*)-carboxylate**

5 A solution of NBS (0.29 g, 1.6 mmol) in DMF (2.0 mL) was added dropwise to a solution of *tert*-butyl (8a*S*,12a*R*)-4,5,6,7,9,10,12,12a-octahydroazepino[3,2,1-*hi*]pyrido[4,3-*b*]indole-11(8a*H*)-carboxylate (0.53 g, 1.6 mmol) in DMF (3.0 mL) at 0 °C. The mixture was stirred at 0 °C for 15 min and room temperature for 0.5 h before poured into water (10 mL). The milky mixture was extracted with EtOAc (3 ×
10 10 mL) and the extract was dried (MgSO₄), concentrated *in vacuo* and flash column chromatography (EtOAc:hexane / 1:4) gave the title compound (0.58 g, 89%) as a white solid.

EXAMPLE 315

15 **(8a*S*,12a*R*)-2-(2,4-dichlorophenyl)-4,5,6,7,8a,9,10,11,12,12a-decahydroazepino[3,2,1-*hi*]pyrido[4,3-*b*]indole**

Step A:

A mixture of *tert*-butyl (8a*S*,12a*R*)-2-bromo-4,5,6,7,9,10,12,12a-octahydroazepino[3,2,1-*hi*]pyrido[4,3-*b*]indole-11(8a*H*)-carboxylate (0.20 g, 0.50
20 mmol), 2,4-dichlorophenylboronic acid (0.19 g, 1.0 mmol), Ba(OH)₂·8H₂O (0.32 g, 1.0 mmol), Pd₂(dba)₃ (7.5 mg, 0.0075 mmol) and PPh₃ (5.24 mg, 0.02 mmol) in DME (10 mL) and water (2.5 mL) was degassed and refluxed for 18 h and cooled to room temperature. The mixture was concentrated *in vacuo* and EtOAc (20 mL) was
25 added. The solution was washed with saturated Na₂CO₃ (2 × 10 mL), dried (Na₂SO₄), concentrated *in vacuo* and flash column chromatography (EtOAc:hexane / 1:9) gave *tert*-butyl (8a*S*,12a*R*)-2-(2,4-dichlorophenyl)-4,5,6,7,8a,9,10,11,12,12a-decahydroazepino[3,2,1-*hi*]pyrido[4,3-*b*]indole-11(8a*H*)-carboxylate (0.16 g, 66%) as a white foam.

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Step B:

The title compound (0.087 g, 77%) was prepared by the general method of Example 312, step B from *tert*-butyl (8a*S*,12a*R*)-2-(2,4-dichlorophenyl)-4,5,6,7,8a,9,10,11,12,12a-decahydroazepino[3,2,1-*hi*]pyrido[4,3-*b*]indole-11(8a*H*)-carboxylate (0.14 g, 0.30 mmol) as a white foam. ¹H NMR (CDCl₃, 300 MHz) δ 1.50-1.70 (m, 1H), 1.70-1.90 (m, 2H), 1.90-2.10 (m, 4H), 2.48-2.80 (m, 3H), 2.80-3.00 (m, 3H), 3.04 (dd, J = 6.3, 12.4 Hz, 1H), 3.10-3.25 (m, 1H), 3.25-3.42 (m, 2H), 6.96 (s, 1H), 7.00 (s, 1H), 7.20-7.30 (m, 2H), 7.44 (d, J = 1.1 Hz, 1H) ppm.

EXAMPLE 316

(8a*S*,12a*R*)-2-(2,3-dichlorophenyl)-4,5,6,7,8a,9,10,11,12,12a-decahydroazepino[3,2,1-*hi*]pyrido[4,3-*b*]indole

Step A:

Tert-butyl (8a*S*,12a*R*)-2-(2,3-dichlorophenyl)-4,5,6,7,8a,9,10,11,12,12a-decahydroazepino[3,2,1-*hi*]pyrido[4,3-*b*]indole-11(8a*H*)-carboxylate (0.14 g, 59%) was prepared by the general method of Example 89, step C from *tert*-butyl (8a*S*,12a*R*)-2-bromo-4,5,6,7,9,10,12,12a-octahydroazepino[3,2,1-*hi*]pyrido[4,3-*b*]indole-11(8a*H*)-carboxylate (0.20 g, 0.50 mmol), 2,3-dichlorophenyl boronic acid (0.19 g, 1.0 mmol), Pd(PPh₃)₂Cl₂ (17 mg, 0.025 mmol), Na₂CO₃ (2.0 M, 1.0 mL, 2.0 mmol) as a white foam.

Step B:

The title compound (0.10 g, 92%) was prepared by the general method of Example 312, step B from *tert*-butyl (8a*S*,12a*R*)-2-(2,3-dichlorophenyl)-4,5,6,7,8a,9,10,11,12,12a-decahydroazepino[3,2,1-*hi*]pyrido[4,3-*b*]indole-11(8a*H*)-carboxylate (0.14 g, 0.30 mmol) as a white foam. ¹H NMR (CDCl₃, 300 MHz) δ 1.50-1.70 (m, 1H), 1.70-1.92 (m, 2H), 1.92-2.08 (m, 3H), 2.15-2.80 (m, 4H), 2.80-3.00 (m, 3H), 3.05 (dd, J = 6.3, 12.4 Hz, 1H), 3.10-3.34 (m, 2H), 3.34-3.42 (m, 1H), 6.96 (d, J = 1.6 Hz, 1H), 7.00 (d, J = 1.6 Hz, 1H), 7.12-7.25 (m, 2H), 7.38 (dd, J = 2.4, 7.2 Hz, 1H) ppm. MS (ESI): 373 (base, M+H).

EXAMPLE 317

(8a*S*,12a*R*)-2-(3,4-dichlorophenyl)-4,5,6,7,8a,9,10,11,12,12a-decahydroazepino[3,2,1-*hi*]pyrido[4,3-*b*]indole

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Step A:

Tert-butyl (8a*S*,12a*R*)-2-(3,4-dichlorophenyl)-4,5,6,7,8a,9,10,11,12,12a-decahydroazepino[3,2,1-*hi*]pyrido[4,3-*b*]indole-11(8a*H*)-carboxylate (0.070 g, 30%) was prepared by the general method of Example 89, step C from *tert*-butyl

10 (8a*S*,12a*R*)-2-bromo-4,5,6,7,9,10,12,12a-octahydroazepino[3,2,1-*hi*]pyrido[4,3-*b*]indole-11(8a*H*)-carboxylate (0.20 g, 0.50 mmol), 3,4-dichlorophenyl boronic acid (0.19 g, 1.0 mmol), Pd(PPh₃)₂Cl₂ (17 mg, 0.025 mmol), Na₂CO₃ (2.0 M, 1.0 mL, 2.0 mmol) as a white foam.

15 **Step B:**

The title compound (0.040 g, 72%) was prepared by the general method of Example 312, step B from *tert*-butyl (8a*S*,12a*R*)-2-(3,4-dichlorophenyl)-4,5,6,7,8a,9,10,11,12,12a-decahydroazepino[3,2,1-*hi*]pyrido[4,3-*b*]indole-11(8a*H*)-carboxylate (0.070 g, 0.15 mmol) as a white foam. ¹H NMR (CDCl₃, 300 MHz) δ

20 1.50-1.70 (m, 1H), 1.70-1.92 (m, 2H), 1.92-2.10 (m, 3H), 2.23 (br, 1H), 2.48-2.80 (m, 3H), 2.80-3.00 (m, 3H), 3.06 (dd, J = 6.3, 12.4 Hz, 1H), 3.14-3.25 (m, 1H), 3.25-3.40 (m, 2H), 7.11 (s, 2H), 7.35 (dd, J = 2.2, 8.4 Hz, 1H), 7.42 (d, J = 8.4 Hz, 1H), 7.61 (d, J = 2.2 Hz, 1H) ppm.

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EXAMPLE 318

(8a*S*,12a*R*)-2-(3,5-dichlorophenyl)-4,5,6,7,8a,9,10,11,12,12a-decahydroazepino[3,2,1-*hi*]pyrido[4,3-*b*]indole**Step A:**

30 *Tert*-butyl (8a*S*,12a*R*)-2-(3,5-dichlorophenyl)-4,5,6,7,8a,9,10,11,12,12a-decahydroazepino[3,2,1-*hi*]pyrido[4,3-*b*]indole-11(8a*H*)-carboxylate (0.13 g, 55%)

was prepared by the general method of Example 89, step C from *tert*-butyl (8a*S*,12a*R*)-2-bromo-4,5,6,7,9,10,12,12a-octahydroazepino[3,2,1-*hi*]pyrido[4,3-*b*]indole-11(8a*H*)-carboxylate (0.20 g, 0.50 mmol), 3,5-dichlorophenyl boronic acid (0.19 g, 1.0 mmol), Pd(PPh₃)₂Cl₂ (17 mg, 0.025 mmol), Na₂CO₃ (2.0 M, 1.0 mL, 2.0 mmol) as a white foam. MS (ESI): 473 (base, M+H).

Step B:

The title compound (0.10 g, 92%) was prepared by the general method of Example 312, step B from *tert*-butyl (8a*S*,12a*R*)-2-(3,5-dichlorophenyl)-4,5,6,7,8a,9,10,11,12,12a-decahydroazepino[3,2,1-*hi*]pyrido[4,3-*b*]indole-11(8a*H*)-carboxylate (0.14 g, 0.30 mmol) as a white foam. ¹H NMR (CDCl₃, 300 MHz) δ 1.50-1.70 (m, 1H), 1.70-1.90 (m, 2H), 1.90-2.15 (m, 5H), 2.48-65 (m, 2H), 2.65-2.80 (m, 1H), 2.82-2.90 (m, 2H), 3.07 (dd, J = 6.3, 12.4 Hz, 1H), 3.12-3.26 (m, 1H), 3.26-3.40 (m, 2H), 7.10 (s, 2H), 7.22 (t, J = 1.8 Hz, 2H), 7.39 (d, J = 1.8 Hz, 2H) ppm. MS (ESI): 373 (base, M+H).

EXAMPLE 319

(8a*S*,12a*R*)-2-(2,5-dichlorophenyl)-4,5,6,7,8a,9,10,11,12,12a-decahydroazepino[3,2,1-*hi*]pyrido[4,3-*b*]indole

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Step A:

A mixture of *tert*-butyl (8a*S*,12a*R*)-2-bromo-4,5,6,7,9,10,12,12a-octahydroazepino[3,2,1-*hi*]pyrido[4,3-*b*]indole-11(8a*H*)-carboxylate (0.10 g, 0.25 mmol), 2,5-dichlorophenyl boronic acid (0.10 g, 0.50 mmol) and Ba(OH)₂ (0.17 M, 3.0 mL, 0.51 mmol) in DME (15 mL) was degassed at 40-50 °C before Pd(PPh₃)₄ (12 mg, 0.010 mmol) was added. The mixture was degassed again as described before and refluxed for 16 h. The mixture was concentrated *in vacuo* and EtOAc (20 mL) was added. The solution was washed with saturated Na₂CO₃ (2 × 10 mL), dried (Na₂SO₄), concentrated *in vacuo* and flash column chromatography (EtOAc:hexane / 1:9) gave *tert*-butyl (8a*S*,12a*R*)-2-(2,5-dichlorophenyl)-4,5,6,7,8a,9,10,11,12,12a-

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decahydroazepino[3,2,1-*hi*]pyrido[4,3-*b*]indole-11(8a*H*)-carboxylate (0.098 g, 83%) as a white foam. MS (ESI): 473 (base, M+H).

Step B:

5 The title compound (0.077 g, 100%) was prepared by the general method of Example 312, step B from *tert*-butyl (8a*S*,12a*R*)-2-(2,5-dichlorophenyl)-4,5,6,7,8a,9,10,11,12,12a-decahydroazepino[3,2,1-*hi*]pyrido[4,3-*b*]indole-11(8a*H*)-carboxylate (0.098 g, 0.21 mmol) as a white foam. ¹H NMR (CDCl₃, 300 MHz) δ 1.50-1.70 (m, 2H), 1.70-1.90 (m, 2H), 1.90-2.10 (m, 3H), 2.48-2.80 (m, 3H), 2.85-
10 3.00 (m, 3H), 3.08 (dd, J = 6.3, 12.4 Hz, 1H), 3.15-3.35 (m, 2H), 3.35-3.44 (m, 1H), 6.98 (s, 1H), 7.02 (s, 1H), 7.18 (dd, J = 2.6, 8.6 Hz, 1H), 7.32 (d, J = 2.6 Hz, 1H), 7.35 (d, J = 8.6 Hz, 1H) ppm. MS (ESI): 373 (base, M+H).

EXAMPLE 320

15 **(8a*S*,12a*R*)-2-(2,6-dichlorophenyl)-4,5,6,7,8a,9,10,11,12,12a-decahydroazepino[3,2,1-*hi*]pyrido[4,3-*b*]indole**

Step A:

20 A mixture of *tert*-butyl (8a*S*,12a*R*)-2-bromo-4,5,6,7,9,10,12,12a-octahydroazepino[3,2,1-*hi*]pyrido[4,3-*b*]indole-11(8a*H*)-carboxylate (0.10 g, 0.25 mmol), 2,6-dichlorophenylboronic acid (0.10 g, 0.50 mmol), Pd(dppf)₂Cl₂ (10 mg, 0.012 mmol) and TEA (1.0 mL, 7.2 mmol) in DME (15 mL) was degassed at 40-50 °C and refluxed for 32 h. The mixture was concentrated *in vacuo* and EtOAc (20 mL) was added. The solution was washed with saturated Na₂CO₃ (2 × 10 mL), dried
25 (Na₂SO₄) and concentrated *in vacuo*. Normal phase HPLC (5% EtOAc in hexane) gave *tert*-butyl (8a*S*,12a*R*)-2-(2,6-dichlorophenyl)-4,5,6,7,8a,9,10,11,12,12a-decahydroazepino[3,2,1-*hi*]pyrido[4,3-*b*]indole-11(8a*H*)-carboxylate (0.030 g, 26%) as a white foam. MS (ESI): 473 (base, M+H).

Step B:

The title compound (0.025 g, 100%) was prepared by the general method of Example 312, step B from *tert*-butyl (8a*S*,12a*R*)-2-(2,6-dichlorophenyl)-4,5,6,7,8a,9,10,11,12,12a-decahydroazepino[3,2,1-*hi*]pyrido[4,3-*b*]indole-11(8a*H*)-carboxylate (0.030 g, 0.060 mmol) as a white foam. ¹H NMR (CDCl₃, 300 MHz) δ 1.50-1.70 (m, 1H), 1.70-1.88 (m, 2H), 1.88-2.10 (m, 3H), 2.48-2.80 (m, 4H), 2.82-3.00 (m, 3H), 3.06 (dd, J = 6.3, 12.4 Hz, 1H), 3.15-3.38 (m, 2H), 3.38-3.44 (m, 1H), 6.79 (s, 2H), 7.14 (t, J = 8.0 Hz, 1H), 7.35 (d, J = 8.0 Hz, 2H) ppm. MS (ESI): 373 (base, M+H).

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EXAMPLE 321

(8a*S*,12a*R*)-2-(2-chlorophenyl)-4,5,6,7,8a,9,10,11,12,12a-decahydroazepino[3,2,1-*hi*]pyrido[4,3-*b*]indole

Step A:

Tert-butyl (8a*S*,12a*R*)-2-(2-chlorophenyl)-4,5,6,7,8a,9,10,11,12,12a-decahydroazepino[3,2,1-*hi*]pyrido[4,3-*b*]indole-11(8a*H*)-carboxylate (0.15 g, 67%) was prepared by the general method of Example 89, step C from *tert*-butyl (8a*S*,12a*R*)-2-bromo-4,5,6,7,9,10,12,12a-octahydroazepino[3,2,1-*hi*]pyrido[4,3-*b*]indole-11(8a*H*)-carboxylate (0.20 g, 0.50 mmol), 2-chlorophenylboronic acid (0.16 g, 1.0 mmol), Pd(PPh₃)₂Cl₂ (17 mg, 0.025 mmol), Na₂CO₃ (2.0 M, 1.0 mL, 2.0 mmol) as a white foam. MS (ESI): 439 (base, M+H).

20

Step B:

The title compound (0.087 g, 77%) was prepared by the general method of Example 312, step B from *tert*-butyl (8a*S*,12a*R*)-2-(2-chlorophenyl)-4,5,6,7,8a,9,10,11,12,12a-decahydroazepino[3,2,1-*hi*]pyrido[4,3-*b*]indole-11(8a*H*)-carboxylate (0.15 g, 0.33 mmol) as a white foam. ¹H NMR (CDCl₃, 300 MHz) δ 1.50-1.70 (m, 1H), 1.70-2.10 (m, 5H), 2.48-2.78 (m, 3H), 2.88-3.02 (m, 3H), 3.10 (dd, J = 6.3, 12.4 Hz, 1H), 3.20-3.35 (m, 2H), 3.35-3.42 (m, 1H), 3.63 (br, 1H), 7.01 (s,

30

1H), 7.05 (s, 1H), 7.15-7.35 (m, 3H), 7.43 (dd, J = 1.7, 7.5 Hz, 1H) ppm. MS (ESI): 339 (base, M+H).

EXAMPLE 322

5 (8a*S*,12a*R*)-2-(3-chlorophenyl)-4,5,6,7,8a,9,10,11,12,12a-decahydroazepino[3,2,1-*hi*]pyrido[4,3-*b*]indole

Step A:

Tert-butyl (8a*S*,12a*R*)-2-(3-chlorophenyl)-4,5,6,7,8a,9,10,11,12,12a-decahydroazepino[3,2,1-*hi*]pyrido[4,3-*b*]indole-11(8a*H*)-carboxylate (0.12 g, 55%)
10 was prepared by the general method of Example 89, step C from *tert*-butyl (8a*S*,12a*R*)-2-bromo-4,5,6,7,9,10,12,12a-octahydroazepino[3,2,1-*hi*]pyrido[4,3-*b*]indole-11(8a*H*)-carboxylate (0.20 g, 0.50 mmol), 3-chlorophenylboronic acid (0.16 g, 1.0 mmol), Pd(PPh₃)₂Cl₂ (17 mg, 0.025 mmol), Na₂CO₃ (2.0 M, 1.0 mL, 2.0
15 mmol) as a white foam. MS (ESI): 439 (base, M+H).

Step B:

The title compound (0.045 g, 100%) was prepared by the general method of Example 312, step B from *tert*-butyl (8a*S*,12a*R*)-2-(3-chlorophenyl)-
20 4,5,6,7,8a,9,10,11,12,12a-decahydroazepino[3,2,1-*hi*]pyrido[4,3-*b*]indole-11(8a*H*)-carboxylate (0.058 g, 0.13 mmol) as a white foam. ¹H NMR (CDCl₃, 300 MHz) δ 1.43 (br, 1H), 1.50-1.70 (m, 1H), 1.70-2.10 (m, 5H), 2.40-2.80 (m, 3H), 2.80-3.00 (m, 3H), 3.08 (dd, J = 6.3, 12.4 Hz, 1H), 3.10-3.42 (m, 3H), 7.14 (s, 2H), 7.21 (d, J = 7.5 Hz, 1H), 7.30 (t, J = 7.8 Hz, 1H), 7.41 (d, J = 7.8 Hz, 1H), 7.52 (s, 1H) ppm. MS
25 (ESI): 339 (base, M+H).

EXAMPLE 323

(8a*S*,12a*R*)-2-(4-chlorophenyl)-4,5,6,7,8a,9,10,11,12,12a-decahydroazepino[3,2,1-*hi*]pyrido[4,3-*b*]indole

5 Step A:

Tert-butyl (8a*S*,12a*R*)-2-(4-chlorophenyl)-4,5,6,7,8a,9,10,11,12,12a-decahydroazepino[3,2,1-*hi*]pyrido[4,3-*b*]indole-11(8a*H*)-carboxylate (0.11 g, 50%) was prepared by the general method of Example 89, step C from *tert*-butyl (8a*S*,12a*R*)-2-bromo-4,5,6,7,9,10,12,12a-octahydroazepino[3,2,1-*hi*]pyrido[4,3-*b*]indole-11(8a*H*)-carboxylate (0.20 g, 0.50 mmol), 4-chlorophenylboronic acid (0.16 g, 1.0 mmol), Pd(PPh₃)₂Cl₂ (17 mg, 0.025 mmol), Na₂CO₃ (2.0 M, 1.0 mL, 2.0 mmol) as a white foam. MS (ESI): 439 (base, M+H).

Step B:

15 The title compound (0.084 g, 99%) was prepared by the general method of Example 312, step B from *tert*-butyl (8a*S*,12a*R*)-2-(4-chlorophenyl)-4,5,6,7,8a,9,10,11,12,12a-decahydroazepino[3,2,1-*hi*]pyrido[4,3-*b*]indole-11(8a*H*)-carboxylate (0.11 g, 0.25 mmol) as a white foam. ¹H NMR (CDCl₃, 300 MHz) δ 1.50-1.70 (m, 1H), 1.70-2.10 (m, 5H), 2.48-2.80 (m, 3H), 2.80-3.05 (m, 4H), 3.12 (dd, J = 6.3, 12.4 Hz, 1H), 3.20-3.42 (m, 3H), 7.14 (s, 2H), 7.36 (d, J = 8.4 Hz, 2H), 7.46 (d, J = 8.4 Hz, 2H) ppm. MS (ESI): 339 (base, M+H).

EXAMPLE 324

25 **(±)-*cis*-2-(2,6-difluorophenyl)-4,5,6,7,8a,9,10,11,12,12a-decahydroazepino[3,2,1-*hi*]pyrido[4,3-*b*]indole**

Step A:

30 *Tert*-butyl (±)-2-(2,6-difluorophenyl)-4,5,6,7,8a,9,10,11,12,12a-decahydroazepino[3,2,1-*hi*]pyrido[4,3-*b*]indole-11(8a*H*)-carboxylate (0.045 g, 21%) was prepared by the general method of Example 320, step A from *tert*-butyl (±)-2-bromo-4,5,6,7,9,10,12,12a-octahydroazepino[3,2,1-*hi*]pyrido[4,3-*b*]indole-11(8a*H*)-

carboxylate (0.20 g, 0.50 mmol), 2,6-difluorophenylboronic acid (0.32 g, 2.0 mmol), Pd(dppf)₂Cl₂ (24 mg, 0.030 mmol), TEA (1.6 mL, 11 mmol) as a white foam.

Step B:

5 The title compound (0.017 g, 49%) was prepared by the general method of Example 312, step B from *tert*-butyl (8a*S*,12a*R*)-2-(2,6-difluorophenyl)-4,5,6,7,8a,9,10,11,12,12a-decahydroazepino[3,2,1-*hi*]pyrido[4,3-*b*]indole-11(8a*H*)-carboxylate (0.045 g, 0.10 mmol) as a white foam. ¹H NMR (CDCl₃, 300 MHz) δ 1.50-1.70 (m, 1H), 1.70-2.10 (m, 5H), 2.50-2.80 (m, 3H), 2.80-3.05 (m, 3H), 3.05-10 3.20 (m, 2H), 3.20-3.35 (m, 2H), 3.35-3.42 (m, 1H), 6.94 (t, J = 8.1 Hz, 2H), 7.04 (s, 2H), 7.15-7.22 (m, 1H) ppm.

EXAMPLE 325

(8a*S*,12a*R*)-2-(2,6-difluorophenyl)-4,5,6,7,8a,9,10,11,12,12a-
15 decahydroazepino[3,2,1-*hi*]pyrido[4,3-*b*]indole

Step A:

Tert-butyl (8a*S*,12a*R*)-2-(2,6-difluorophenyl)-4,5,6,7,8a,9,10,11,12,12a-decahydroazepino[3,2,1-*hi*]pyrido[4,3-*b*]indole-11(8a*H*)-carboxylate (0.040 g, 18%)
20 was prepared by the general method of Example 320, step A from *tert*-butyl (8a*S*,11a*R*)-2-bromo-4,5,6,7,9,10,12,12a-octahydroazepino[3,2,1-*hi*]pyrido[4,3-*b*]indole-11(8a*H*)-carboxylate (0.20 g, 0.50 mmol), 2,6-difluorophenylboronic acid (0.32 g, 2.0 mmol), Pd(dppf)₂Cl₂ (24 mg, 0.030 mmol), TEA (1.6 mL, 11 mmol) as a white foam.

25 **Step B:**

The title compound (9.0 mg, 29%) was prepared by the general method of Example 312, step B from *tert*-butyl (8a*S*,12a*R*)-2-(2,6-difluorophenyl)-4,5,6,7,8a,9,10,11,12,12a-decahydroazepino[3,2,1-*hi*]pyrido[4,3-*b*]indole-11(8a*H*)-carboxylate (0.040 g, 0.091 mmol) as a white foam. ¹H NMR was identical to that of
30 (±)-*cis*-2-(2,6-difluorophenyl)-4,5,6,7,8a,9,10,11,12,12a-decahydroazepino[3,2,1-*hi*]pyrido[4,3-*b*]indole

EXAMPLE 326

(8a*S*,12a*R*)-2-(2,3-difluorophenyl)-4,5,6,7,8a,9,10,11,12,12a-decahydroazepino[3,2,1-*hi*]pyrido[4,3-*b*]indole

5

Step A:

Tert-butyl (8a*S*,12a*R*)-2-(2,3-difluorophenyl)-4,5,6,7,8a,9,10,11,12,12a-decahydroazepino[3,2,1-*hi*]pyrido[4,3-*b*]indole-11(8a*H*)-carboxylate (0.069 g, 63%) was prepared by the general method of Example 319, step A from *tert*-butyl

10 (8a*S*,12a*R*)-2-bromo-4,5,6,7,9,10,12,12a-octahydroazepino[3,2,1-*hi*]pyrido[4,3-*b*]indole-11(8a*H*)-carboxylate (0.10 g, 0.25 mmol), 2,3-difluorophenylboronic acid (0.080 g, 0.5 mmol), Pd(PPh₃)₄ (12 mg, 0.010 mmol), and Ba(OH)₂ (0.17 M, 3.0 mL, 0.51 mmol) as a white foam. MS (ESI): 441 (base, M+H).

15 Step B:

The title compound (0.053 g, 100%) was prepared by the general method of Example 312, step B from *tert*-butyl (8a*S*,12a*R*)-2-(2,3-difluorophenyl)-4,5,6,7,8a,9,10,11,12,12a-decahydroazepino[3,2,1-*hi*]pyrido[4,3-*b*]indole-11(8a*H*)-carboxylate (0.069 g, 0.16 mmol) as a white foam. ¹H NMR (CDCl₃, 300 MHz) δ

20 1.50-1.70 (m, 1H), 1.70-2.10 (m, 5H), 2.48-2.80 (m, 3H), 2.85-3.02 (m, 3H), 3.12 (dd, J = 6.3, 12.4 Hz, 1H), 3.20-3.60 (m, 4H), 7.00-7.22 (m, 5H) ppm. MS (ESI): 341 (base, M+H).

EXAMPLE 327

25 (8a*S*,12a*R*)-2-(3,4-difluorophenyl)-4,5,6,7,8a,9,10,11,12,12a-decahydroazepino[3,2,1-*hi*]pyrido[4,3-*b*]indole

Step A:

Tert-butyl (8a*S*,12a*R*)-2-(3,4-difluorophenyl)-4,5,6,7,8a,9,10,11,12,12a-decahydroazepino[3,2,1-*hi*]pyrido[4,3-*b*]indole-11(8a*H*)-carboxylate (0.078 g, 71%) was prepared by the general method of Example 319, step A from *tert*-butyl

30

(8a*S*,12a*R*)-2-bromo-4,5,6,7,9,10,12,12a-octahydroazepino[3,2,1-*hi*]pyrido[4,3-*b*]indole-11(8a*H*)-carboxylate (0.10 g, 0.25 mmol), 3,4-difluorophenylboronic acid (0.080 g, 0.50 mmol), Pd(PPh₃)₄ (12 mg, 0.010 mmol), and Ba(OH)₂ (0.17 M, 3.0 mL, 0.51 mmol) as a white foam. MS (ESI): 441 (base, M+H).

5

Step B:

The title compound (0.055 g, 92%) was prepared by the general method of Example 312, step B from *tert*-butyl (8a*S*,12a*R*)-2-(3,4-difluorophenyl)-4,5,6,7,8a,9,10,11,12,12a-decahydroazepino[3,2,1-*hi*]pyrido[4,3-*b*]indole-11(8a*H*)-carboxylate (0.078 g, 0.18 mmol) as a white foam. ¹H NMR (CDCl₃, 300 MHz) δ 1.50-1.70 (m, 1H), 1.70-2.12 (m, 5H), 2.50-2.80 (m, 3H), 2.92-3.05 (m, 3H), 3.14 (dd, J = 6.3, 12.4 Hz, 1H), 3.22-3.42 (m, 3H), 3.49 (s, 1H), 7.05-7.40 (m, 5H) ppm. MS (ESI): 341 (base, M+H).

15

EXAMPLE 328

(8a*S*,12a*R*)-2-(3-fluorophenyl)-4,5,6,7,8a,9,10,11,12,12a-decahydroazepino[3,2,1-*hi*]pyrido[4,3-*b*]indole

Step A:

Tert-butyl (8a*S*,12a*R*)-2-(3-fluorophenyl)-4,5,6,7,8a,9,10,11,12,12a-decahydroazepino[3,2,1-*hi*]pyrido[4,3-*b*]indole-11(8a*H*)-carboxylate (0.13 g, 62%) was prepared by the general method of Example 89, step C from *tert*-butyl (8a*S*,12a*R*)-2-bromo-4,5,6,7,9,10,12,12a-octahydroazepino[3,2,1-*hi*]pyrido[4,3-*b*]indole-11(8a*H*)-carboxylate (0.20 g, 0.50 mmol), 3-fluorophenylboronic acid (0.14 g, 1.0 mmol), Pd(PPh₃)₂Cl₂ (17 mg, 0.025 mmol), Na₂CO₃ (2.0 M, 1.0 mL, 2.0 mmol) as a white foam. MS (ESI): 423 (base, M+H).

25

Step B:

The title compound (0.025 g, 93%) was prepared by the general method of Example 312, step B from *tert*-butyl (8a*S*,12a*R*)-2-(3-fluorophenyl)-4,5,6,7,8a,9,10,11,12,12a-decahydroazepino[3,2,1-*hi*]pyrido[4,3-*b*]indole-11(8a*H*)-

30

carboxylate (0.035 g, 0.083 mmol) as a white foam. ^1H NMR (CDCl_3 , 300 MHz) δ 1.50-1.70 (m, 1H), 1.70-2.17 (m, 6H), 2.48-2.82 (m, 3H), 2.82-3.05 (m, 3H), 3.08 (dd, $J = 6.3, 12.4$ Hz, 1H), 3.15-3.40 (m, 3H), 6.88-6.96 (m, 1H), 7.15 (s, 2H), 7.18-7.26 (m, 1H), 7.28-7.35 (m, 2H) ppm. MS (ESI): 323 (base, $\text{M}+\text{H}$).

5

EXAMPLE 329

(8a*S*,12a*R*)-2-[2-chloro-4-(trifluoromethyl)phenyl]-4,5,6,7,8a,9,10,11,12,12a-decahydroazepino[3,2,1-*hi*]pyrido[4,3-*b*]indole

10 **Step A:**

Tert-butyl (8a*S*,12a*R*)-2-[2-chloro-4-(trifluoromethyl)phenyl]-4,5,6,7,8a,9,10,11,12,12a-decahydroazepino[3,2,1-*hi*]pyrido[4,3-*b*]indole-11(8a*H*)-carboxylate (0.21 g, 82%) was prepared by the general method of Example 89, step C from *tert-butyl* (8a*S*,12a*R*)-2-bromo-4,5,6,7,9,10,12,12a-octahydroazepino[3,2,1-*hi*]pyrido[4,3-*b*]indole-11(8a*H*)-carboxylate (0.20 g, 0.50 mmol), 2-chloro-4-(trifluoromethyl)phenylboronic acid (0.22 g, 1.0 mmol), $\text{Pd}(\text{PPh}_3)_2\text{Cl}_2$ (17 mg, 0.025 mmol), Na_2CO_3 (2.0 M, 1.0 mL, 2.0 mmol) as a white foam.

15

Step B:

The title compound (0.15 g, 87%) was prepared by the general method of Example 312, step B from *tert-butyl* (8a*S*,12a*R*)-2-[2-chloro-4-(trifluoromethyl)phenyl]-4,5,6,7,8a,9,10,11,12,12a-decahydroazepino[3,2,1-*hi*]pyrido[4,3-*b*]indole-11(8a*H*)-carboxylate (0.21 g, 0.41 mmol) as a white foam. ^1H NMR (CDCl_3 , 300 MHz) δ 1.50-1.70 (m, 1H), 1.70-1.90 (m, 2H), 1.90-2.20 (m, 4H), 2.48-2.80 (m, 3H), 2.80-3.00 (m, 3H), 3.05 (dd, $J = 6.3, 12.4$ Hz, 1H), 3.10-3.25 (m, 1H), 3.25-3.36 (m, 1H), 3.36-3.45 (m, 1H), 7.00 (d, $J = 1.5$ Hz, 1H), 7.05 (d, $J = 1.5$ Hz, 1H), 7.44 (d, $J = 8.1$ Hz, 1H), 7.51 (dd, $J = 1.1, 8.1$ Hz, 1H), 7.70 (s, 1H) ppm.

25

EXAMPLE 330

(8a*S*,12a*R*)-2-(2-chloro-4-methoxyphenyl)-4,5,6,7,8a,9,10,11,12,12a-decahydroazepino[3,2,1-*hi*]pyrido[4,3-*b*]indole5 **Step A:**

Tert-butyl (8a*S*,12a*R*)-2-(2-chloro-4-methoxyphenyl)-4,5,6,7,8a,9,10,11,12,12a-decahydroazepino[3,2,1-*hi*]pyrido[4,3-*b*]indole-11(8a*H*)-carboxylate (0.15 g, 64%) was prepared by the general method of Example 89, step C from *tert-butyl* (8a*S*,12a*R*)-2-bromo-4,5,6,7,9,10,12,12a-octahydroazepino[3,2,1-*hi*]pyrido[4,3-*b*]indole-11(8a*H*)-carboxylate (0.20 g, 0.50 mmol), 2-chloro-4-methoxyphenylboronic acid (0.19 g, 1.0 mmol), Pd(PPh₃)₂Cl₂ (17 mg, 0.025 mmol), Na₂CO₃ (2.0 M, 1.0 mL, 2.0 mmol) as a white foam.

Step B:

15 The title compound (0.12 g, 97%) was prepared by the general method of Example 312, step B from *tert-butyl* (8a*S*,12a*R*)-2-(2-chloro-4-methoxyphenyl)-4,5,6,7,8a,9,10,11,12,12a-decahydroazepino[3,2,1-*hi*]pyrido[4,3-*b*]indole-11(8a*H*)-carboxylate (0.15 g, 0.32 mmol) as a white foam. ¹H NMR (CDCl₃, 300 MHz) δ 1.50-1.70 (m, 1H), 1.70-1.85 (m, 2H), 1.90-2.10 (m, 3H), 2.10-2.30 (m, 2H), 2.48-2.72 (m, 3H), 2.88-3.00 (m, 1H), 3.08-3.40 (m, 4H), 3.48-3.58 (m, 1H), 3.81 (s, 3H), 6.82 (dd, J = 2.4, 8.4 Hz, 1H), 6.92-7.05 (m, 3H), 7.19 (d, J = 8.4 Hz, 1H) ppm.

EXAMPLE 331

(8a*S*,12a*R*)-2-(2-fluoro-4-methoxyphenyl)-4,5,6,7,8a,9,10,11,12,12a-decahydroazepino[3,2,1-*hi*]pyrido[4,3-*b*]indole**Step A:**

Tert-butyl (8a*S*,12a*R*)-2-(2-fluoro-4-methoxyphenyl)-4,5,6,7,8a,9,10,11,12,12a-decahydroazepino[3,2,1-*hi*]pyrido[4,3-*b*]indole-11(8a*H*)-carboxylate (0.16 g, 69%) was prepared by the general method of Example 89, step C from *tert-butyl* (8a*S*,12a*R*)-2-bromo-4,5,6,7,9,10,12,12a-octahydroazepino[3,2,1-

hi]pyrido[4,3-*b*]indole-11(8*aH*)-carboxylate (0.20 g, 0.50 mmol), 2-fluoro-4-methoxyphenylboronic acid (0.17 g, 1.0 mmol), Pd(PPh₃)₂Cl₂ (17 mg, 0.025 mmol), Na₂CO₃ (2.0 M, 1.0 mL, 2.0 mmol) as a white foam. MS (ESI): 453 (base, M+H).

5 Step B:

The title compound (0.11 g, 94%) was prepared by the general method of Example 312, step B from *tert*-butyl (8*aS*,12*aR*)-2-(2-fluoro-4-methoxyphenyl)-4,5,6,7,8*a*,9,10,11,12,12*a*-decahydroazepino[3,2,1-*hi*]pyrido[4,3-*b*]indole-11(8*aH*)-carboxylate (0.15 g, 0.34 mmol) as a white foam. ¹H NMR (CDCl₃, 300 MHz) δ

10 1.50-1.70 (m, 1H), 1.70-1.90 (m, 2H), 1.90-2.10 (m, 3H), 2.50-2.80 (m, 3H), 2.80-3.00 (m, 3H), 3.05 (dd, J = 6.3, 12.4 Hz, 1H), 3.10-3.25 (m, 1H), 3.25-3.40 (m, 2H), 3.82 (s, 3H), 6.64-6.76 (m, 2H), 7.07 (s, 1H), 7.08 (s, 1H), 7.31 (t, J = 8.8 Hz, 1H) ppm. MS (ESI): 353 (base, M+H).

15

EXAMPLE 332

(8*aS*,12*aR*)-2-(4-methoxy-2-methylphenyl)-4,5,6,7,8*a*,9,10,11,12,12*a*-decahydroazepino[3,2,1-*hi*]pyrido[4,3-*b*]indole

Step A:

20 *Tert*-butyl (8*aS*,12*aR*)-2-(4-methoxy-2-methylphenyl)-4,5,6,7,8*a*,9,10,11,12,12*a*-decahydroazepino[3,2,1-*hi*]pyrido[4,3-*b*]indole-11(8*aH*)-carboxylate (0.095 g, 42%) was prepared by the general method of Example 89, step C from *tert*-butyl (8*aS*,12*aR*)-2-bromo-4,5,6,7,9,10,12,12*a*-octahydroazepino[3,2,1-*hi*]pyrido[4,3-*b*]indole-11(8*aH*)-carboxylate (0.20 g, 0.50 mmol), 4-methoxy-2-

25 methylphenyl boronic acid (0.17 g, 1.0 mmol), Pd(PPh₃)₂Cl₂ (17 mg, 0.025 mmol), Na₂CO₃ (2.0 M, 1.0 mL, 2.0 mmol) as a white foam. MS (ESI): 449 (base, M+H).

Step B:

The title compound (0.071 g, 96%) was prepared by the general method of

30 Example 312, step B from *tert*-butyl (8*aS*,12*aR*)-2-(4-methoxy-2-methylphenyl)-4,5,6,7,8*a*,9,10,11,12,12*a*-decahydroazepino[3,2,1-*hi*]pyrido[4,3-*b*]indole-11(8*aH*)-

carboxylate (0.095 g, 0.21 mmol) as a white foam. ¹H NMR (CDCl₃, 300 MHz) δ 1.50-1.70 (m, 1H), 1.70-1.92 (m, 2H), 1.92-2.10 (m, 3H), 2.28 (s, 3H), 2.45-2.60 (m, 3H), 2.62-2.78 (m, 1H), 2.85-2.98 (m, 3H), 3.08 (dd, J = 6.3, 12.4 Hz, 1H), 3.12-3.40 (m, 3H), 3.82 (s, 3H), 6.70-6.80 (m, 3H), 6.84 (s, 1H), 6.85 (s, 1H), 7.14 (d, J = 8.4 Hz, 1H) ppm. MS (ESI): 349 (base, M+H).

EXAMPLE 333

(8a*S*,12a*R*)-2-[4-methoxy-2-(trifluoromethyl)phenyl]-4,5,6,7,8a,9,10,11,12,12a-decahydroazepino[3,2,1-*hi*]pyrido[4,3-*b*]indole

10

Step A:

Tert-butyl (8a*S*,12a*R*)-2-[4-methoxy-2-(trifluoromethyl)phenyl]-4,5,6,7,8a,9,10,11,12,12a-decahydroazepino[3,2,1-*hi*]pyrido[4,3-*b*]indole-11(8a*H*)-carboxylate (0.20 g, 78%) was prepared by the general method of Example 89, step C from *tert-butyl* (8a*S*,12a*R*)-2-bromo-4,5,6,7,9,10,12,12a-octahydroazepino[3,2,1-*hi*]pyrido[4,3-*b*]indole-11(8a*H*)-carboxylate (0.20 g, 0.50 mmol), 4-methoxy-2-(trifluoromethyl)phenylboronic acid (0.22 g, 1.0 mmol), Pd(PPh₃)₂Cl₂ (17 mg, 0.025 mmol), Na₂CO₃ (2.0 M, 1.0 mL, 2.0 mmol) as a white foam. MS (ESI): 503 (base, M+H).

20

Step B:

The title compound (0.13 g, 84%) was prepared by the general method of Example 312, step B from *tert-butyl* (8a*S*,12a*R*)-2-[4-methoxy-2-(trifluoromethyl)phenyl]-4,5,6,7,8a,9,10,11,12,12a-decahydroazepino[3,2,1-*hi*]pyrido[4,3-*b*]indole-11(8a*H*)-carboxylate (0.20 g, 0.39 mmol) as a white foam. ¹H NMR (CDCl₃, 300 MHz) δ 1.50-1.70 (m, 1H), 1.70-1.90 (m, 2H), 1.90-2.10 (m, 4H), 2.45-2.62 (m, 2H), 2.62-2.75 (m, 1H), 2.80-2.95 (m, 3H), 3.08 (dd, J = 6.3, 12.4 Hz, 1H), 3.08-3.20 (m, 1H), 3.25-3.40 (m, 2H), 3.86 (s, 3H), 6.83 (s, 1H), 6.85 (s, 1H), 7.03 (dd, J = 2.2, 8.4 Hz, 1H), 7.18-7.25 (m, 2H) ppm. MS (ESI): 403 (base, M+H).

30

EXAMPLE 334

(8a*S*,12a*R*)-2-[2-(trifluoromethyl)phenyl]-4,5,6,7,8a,9,10,11,12,12a-decahydroazepino[3,2,1-*hi*]pyrido[4,3-*b*]indole

5 **Step A:**

Tert-butyl (8a*S*,12a*R*)-2-[2-(trifluoromethyl)phenyl]-4,5,6,7,8a,9,10,11,12,12a-decahydroazepino[3,2,1-*hi*]pyrido[4,3-*b*]indole-11(8a*H*)-carboxylate (0.15 g, 61%) was prepared by the general method of Example 89, step C from *tert*-butyl (8a*S*,12a*R*)-2-bromo-4,5,6,7,9,10,12,12a-octahydroazepino[3,2,1-*hi*]pyrido[4,3-*b*]indole-11(8a*H*)-carboxylate (0.20 g, 0.50 mmol), 2-(trifluoromethyl)phenylboronic acid (0.19 g, 1.0 mmol), Pd(PPh₃)₂Cl₂ (17 mg, 0.025 mmol), Na₂CO₃ (2.0 M, 1.0 mL, 2.0 mmol) as a white foam. MS (ESI): 473 (base, M+H).

Step B:

15 The title compound (0.11 g, 96%) was prepared by the general method of Example 312, step B from *tert*-butyl (8a*S*,12a*R*)-2-[2-(trifluoromethyl)phenyl]-4,5,6,7,8a,9,10,11,12,12a-decahydroazepino[3,2,1-*hi*]pyrido[4,3-*b*]indole-11(8a*H*)-carboxylate (0.15 g, 0.31 mmol) as a white foam. ¹H NMR (CDCl₃, 300 MHz) δ 1.50-1.70 (m, 1H), 1.70-1.92 (m, 2H), 1.92-2.25 (m, 3H), 2.45-2.65 (m, 2H), 2.65-2.80 (m, 1H), 2.80-3.00 (m, 4H), 3.08 (dd, J = 6.3, 12.4 Hz, 1H), 3.12-3.25 (m, 1H), 3.25-3.42 (m, 2H), 6.88 (s, 1H), 6.90 (s, 1H), 7.30-7.45 (m, 2H), 7.52 (t, J = 7.3 Hz, 1H), 7.72 (d, J = 8.0 Hz, 1H) ppm. MS (ESI): 373 (base, M+H).

EXAMPLE 335

25 **(8a*S*,12a*R*)-2-[4-isopropoxy-2-(trifluoromethyl)phenyl]-4,5,6,7,8a,9,10,11,12,12a-decahydroazepino[3,2,1-*hi*]pyrido[4,3-*b*]indole**

Step A:

30 *Tert-butyl* (8a*S*,12a*R*)-2-[4-isopropoxy-2-(trifluoromethyl)phenyl]-4,5,6,7,8a,9,10,11,12,12a-decahydroazepino[3,2,1-*hi*]pyrido[4,3-*b*]indole-11(8a*H*)-carboxylate (0.17 g, 63%) was prepared by the general method of Example 89, step C

from *tert*-butyl (8a*S*,12a*R*)-2-bromo-4,5,6,7,9,10,12,12a-octahydroazepino[3,2,1-*hi*]pyrido[4,3-*b*]indole-11(8a*H*)-carboxylate (0.20 g, 0.50 mmol), 4-isopropoxy-2-(trifluoromethyl)phenylboronic acid (0.18 g, 1.0 mmol), Pd(PPh₃)₂Cl₂ (17 mg, 0.025 mmol), Na₂CO₃ (2.0 M, 1.0 mL, 2.0 mmol) as a white foam. MS (ESI): 531 (base, M+H).

Step B:

The title compound (0.14 g, 100%) was prepared by the general method of Example 312, step B from *tert*-butyl (8a*S*,12a*R*)-2-[4-isopropoxy-2-(trifluoromethyl)phenyl]-4,5,6,7,8a,9,10,11,12,12a-decahydroazepino[3,2,1-*hi*]pyrido[4,3-*b*]indole-11(8a*H*)-carboxylate (0.17 g, 0.32 mmol) as a white foam. ¹H NMR (CDCl₃, 300 MHz) δ 1.50-1.70 (m, 1H), 1.39 (d, J = 6.0 Hz, 6H), 1.70-2.10 (m, 5H), 2.45-2.78 (m, 3H), 2.85-3.00 (m, 3H), 3.00-3.10 (m, 1H), 3.12-3.32 (m, 4H), 4.62 (p, J = 6.0 Hz, 1H), 6.86 (s, 1H), 6.87 (s, 1H), 6.98-7.08 (m, 1H), 7.18-7.26 (m, 2H) ppm. MS (ESI): 431 (base, M+H).

EXAMPLE 336

(8a*S*,12a*R*)-2-[2,4-bis(trifluoromethyl)phenyl]-4,5,6,7,8a,9,10,11,12,12a-decahydroazepino[3,2,1-*hi*]pyrido[4,3-*b*]indole

Step A:

Tert-butyl (8a*S*,12a*R*)-2-[2,4-bis(trifluoromethyl)phenyl]-4,5,6,7,8a,9,10,11,12,12a-decahydroazepino[3,2,1-*hi*]pyrido[4,3-*b*]indole-11(8a*H*)-carboxylate (0.047 g, 17%) was prepared by the general method of Example 319, step A from *tert*-butyl (8a*S*,12a*R*)-2-bromo-4,5,6,7,9,10,12,12a-octahydroazepino[3,2,1-*hi*]pyrido[4,3-*b*]indole-11(8a*H*)-carboxylate (0.20 g, 0.50 mmol), 2,4-bis(trifluoromethyl)phenylboronic acid (0.26 g, 1.0 mmol), Pd(PPh₃)₄ (12 mg, 0.010 mmol), and Ba(OH)₂ (2 M, 1.0 mL, 2.0 mmol) as a white foam. MS (ESI): 541 (base, M+H).

Step B:

The title compound (0.038 g, 100%) was prepared by the general method of Example 312, step B from *tert*-butyl (8a*S*,12a*R*)-2-[2,4-bis(trifluoromethyl)phenyl]-4,5,6,7,8a,9,10,11,12,12a-decahydroazepino[3,2,1-*hi*]pyrido[4,3-*b*]indole-11(8a*H*)-carboxylate (0.047 g, 0.087 mmol) as a white foam. ¹H NMR (CDCl₃, 300 MHz) δ 1.40-1.80 (m, 3H), 1.80-2.30 (m, 5H), 2.30-2.72 (m, 3H), 2.72-3.00 (m, 1H), 3.00-3.50 (m, 5H), 6.83 (s, 1H), 6.84 (s, 1H), 7.36 (d, J = 8.3 Hz, 1H), 7.69 (d, J = 8.3 Hz, 1H), 7.87 (s, 1H) ppm. MS (ESI): 441 (base, M+H).

EXAMPLE 337

(8a*S*,12a*R*)-2-[4-fluoro-2-(trifluoromethyl)phenyl]-4,5,6,7,8a,9,10,11,12,12a-decahydroazepino[3,2,1-*hi*]pyrido[4,3-*b*]indole

Step A:

Tert-butyl (8a*S*,12a*R*)-2-[4-fluoro-2-(trifluoromethyl)phenyl]-4,5,6,7,8a,9,10,11,12,12a-decahydroazepino[3,2,1-*hi*]pyrido[4,3-*b*]indole-11(8a*H*)-carboxylate (0.10 g, 84%) was prepared by the general method of Example 319, step A from *tert*-butyl (8a*S*,12a*R*)-2-bromo-4,5,6,7,9,10,12,12a-octahydroazepino[3,2,1-*hi*]pyrido[4,3-*b*]indole-11(8a*H*)-carboxylate (0.10 g, 0.25 mmol), 4-fluoro-2-(trifluoromethyl)phenylboronic acid (0.10 g, 0.50 mmol), Pd(PPh₃)₄ (12 mg, 0.010 mmol), and Ba(OH)₂ (0.17 M, 3.0 mL, 0.51 mmol) as a white foam. MS (ESI): 491 (base, M+H).

Step B:

The title compound (0.042 g, 52%) was prepared by the general method of Example 312, step B from *tert*-butyl (8a*S*,12a*R*)-2-[4-fluoro-2-(trifluoromethyl)phenyl]-4,5,6,7,8a,9,10,11,12,12a-decahydroazepino[3,2,1-*hi*]pyrido[4,3-*b*]indole-11(8a*H*)-carboxylate (0.10 g, 0.21 mmol) as a white foam. ¹H NMR (CDCl₃, 300 MHz) δ 1.50-1.70 (m, 1H), 1.70-2.10 (m, 5H), 2.48-2.65 (m, 2H), 2.65-2.80 (m, 1H), 2.85-3.20 (m, 4H), 3.20-3.42 (m, 4H), 7.10 (s, 2H), 7.20 (t, J = 9.3 Hz, 1H), 6.60-7.70 (m, 1H), 7.70-7.72 (m, 1H) ppm. MS (ESI): 391 (base, M+H).

EXAMPLE 338

4-[(8a*S*,12a*R*)-4,5,6,7,8a,9,10,11,12,12a-decahydroazepino[3,2,1-*hi*]pyrido[4,3-*b*]indol-2-yl]-3-(trifluoromethyl)aniline

5

Step A:

Tert-butyl (8a*S*,12a*R*)-2-[4-[(*tert*-butoxycarbonyl)amino]-2-(trifluoromethyl)phenyl]-4,5,6,7,8a,9,10,11,12,12a-decahydroazepino[3,2,1-*hi*]pyrido[4,3-*b*]indole-11(8a*H*)-carboxylate (0.12 g, 84%) was prepared by the
10 general method of Example 319, step A from *tert*-butyl (8a*S*,12a*R*)-2-bromo-4,5,6,7,9,10,12,12a-octahydroazepino[3,2,1-*hi*]pyrido[4,3-*b*]indole-11(8a*H*)-carboxylate (0.10 g, 0.25 mmol), 4-[(*tert*-butoxycarbonyl)amino]-2-(trifluoromethyl)phenylboronic acid (0.15 g, 0.50 mmol), Pd(PPh₃)₄ (12 mg, 0.010 mmol), and Ba(OH)₂ (0.17 M, 3.0 mL, 0.51 mmol) as a white foam. MS (ESI): 588
15 (base, M+H).

Step B:

The title compound (0.079 g, 98%) was prepared by the general method of Example 312, step B from *tert*-butyl (8a*S*,12a*R*)-2-[4-[(*tert*-butoxycarbonyl)amino]-2-(trifluoromethyl)phenyl]-4,5,6,7,8a,9,10,11,12,12a-decahydroazepino[3,2,1-*hi*]pyrido[4,3-*b*]indole-11(8a*H*)-carboxylate (0.12 g, 0.21 mmol) as a white foam. ¹H
20 NMR (CDCl₃, 300 MHz) δ 1.50-1.70 (m, 2H), 1.70-1.95 (m, 2H), 1.95-2.10 (m, 3H), 2.28-2.76 (m, 3H), 2.80-3.00 (m, 3H), 3.08 (dd, J = 6.3, 12.4 Hz, 1H), 3.10-3.40 (m, 3H), 3.84 (br, 2H), 6.77-6.90 (m, 3H), 7.01 (d, J = 2.6 Hz, 1H), 7.12 (d, J = 8.4 Hz, 1H) ppm. MS (ESI): 388 (lost two BOC groups)(base, M+H).
25

EXAMPLE 339

4-[(8a*S*,12a*R*)-4,5,6,7,8a,9,10,11,12,12a-decahydroazepino[3,2,1-*hi*]pyrido[4,3-*b*]indol-2-yl]-*N*-methyl-3-(trifluoromethyl)aniline

5 **Step A:**

Tert-butyl (8a*S*,12a*R*)-2-[4-[(*tert*-butoxycarbonyl)(methyl)amino]-2-(trifluoromethyl)phenyl]-4,5,6,7,8a,9,10,11,12,12a-decahydroazepino[3,2,1-*hi*]pyrido[4,3-*b*]indole-11(8a*H*)-carboxylate (0.12 g, 81%) was prepared by the general method of Example 319, step A from *tert*-butyl (8a*S*,12a*R*)-2-bromo-
 10 4,5,6,7,9,10,12,12a-octahydroazepino[3,2,1-*hi*]pyrido[4,3-*b*]indole-11(8a*H*)-carboxylate (0.10 g, 0.25 mmol), 4-[(*tert*-butoxycarbonyl)(methyl)amino]-2-(trifluoromethyl)phenylboronic acid (0.16 g, 0.50 mmol), Pd(PPh₃)₄ (12 mg, 0.010 mmol), and Ba(OH)₂ (0.17 M, 3.0 mL, 0.51 mmol) as a white foam. MS (ESI): 602 (base, M+H).

15

Step B:

The title compound (0.081 g, 100%) was prepared by the general method of Example 312, step B from *tert*-butyl (8a*S*,12a*R*)-2-[4-[(*tert*-
 20 butoxycarbonyl)(methyl)amino]-2-(trifluoromethyl)phenyl]-4,5,6,7,8a,9,10,11,12,12a-decahydroazepino[3,2,1-*hi*]pyrido[4,3-*b*]indole-11(8a*H*)-carboxylate (0.12 g, 0.20 mmol) as a white foam. ¹H NMR (CDCl₃, 300 MHz) δ 1.50-1.70 (m, 1H), 1.70-2.10 (m, 5H), 2.48-2.78 (m, 3H), 2.80-3.00 (m, 4H), 3.08 (dd, J = 6.3, 12.4 Hz, 1H), 3.10-3.40 (m, 3H), 3.91 (br, 1H), 6.74 (dd, J = 2.6, 8.2 Hz, 1H), 6.86 (s, 1H), 6.87 (s, 1H), 6.91 (d, J = 2.6 Hz, 1H), 7.15 (d, J = 8.2 Hz, 1H) ppm. MS (ESI): 402 (lost two BOC
 25 groups)(base, M+H).

EXAMPLE 340

2-[(8a*S*,12a*R*)-4,5,6,7,8a,9,10,11,12,12a-decahydroazepino[3,2,1-*hi*]pyrido[4,3-*b*]indol-2-yl]benzaldehyde

5 Step A:

Tert-butyl (8a*S*,12a*R*)-2-(2-formylphenyl)-4,5,6,7,8a,9,10,11,12,12a-decahydroazepino[3,2,1-*hi*]pyrido[4,3-*b*]indole-11(8a*H*)-carboxylate (0.081 g, 38%) was prepared by the general method of Example 89, step C from *tert*-butyl (8a*S*,12a*R*)-2-bromo-4,5,6,7,9,10,12,12a-octahydroazepino[3,2,1-*hi*]pyrido[4,3-*b*]indole-11(8a*H*)-carboxylate (0.20 g, 0.50 mmol), 2-formylphenylboronic acid (0.15 g, 1.0 mmol), Pd(PPh₃)₂Cl₂ (17 mg, 0.025 mmol), Na₂CO₃ (2.0 M, 1.0 mL, 2.0 mmol) as a white foam. MS (ESI): 433 (base, M+H).

Step B:

15 The title compound (0.021 g, 91%) was prepared by the general method of Example 312, step B from *tert*-butyl (8a*S*,12a*R*)-2-(2-formylphenyl)-4,5,6,7,8a,9,10,11,12,12a-decahydroazepino[3,2,1-*hi*]pyrido[4,3-*b*]indole-11(8a*H*)-carboxylate (0.030 g, 0.070 mmol) as a white foam. ¹H NMR (CDCl₃, 300 MHz) δ 1.50-1.88 (m, 3H), 1.90-2.12 (m, 4H), 2.52-2.80 (m, 3H), 2.87-3.04 (m, 3H), 3.08-
20 3.20 (m, 1H), 3.24-3.38 (m, 2H), 3.38-3.44 (m, 1H), 6.93 (s, 1H), 6.97 (s, 1H), 7.38-7.46 (m, 2H), 7.66 (td, J = 7.5, 1.4 Hz, 1H), 7.99 (dd, J = 1.4, 8.0 Hz, 1H), 10.02 (s, 1H) ppm. MS (ESI): 333 (base, M+H).

EXAMPLE 341

25 {2-[(8a*S*,12a*R*)-4,5,6,7,8a,9,10,11,12,12a-decahydroazepino[3,2,1-*hi*]pyrido[4,3-*b*]indol-2-yl]phenyl}methanol

Step A:

NaBH₄ (0.050 g, 1.3 mmol) was added in one portion to a solution of *tert*-
30 butyl (8a*S*,12a*R*)-2-(2-formylphenyl)-4,5,6,7,8a,9,10,11,12,12a-decahydroazepino[3,2,1-*hi*]pyrido[4,3-*b*]indole-11(8a*H*)-carboxylate (0.051 g, 0.12

mmol) in MeOH (12 mL) at room temperature. The mixture was stirred at room temperature for 1 h, quenched with acetone (5.0 mL) and concentrated *in vacuo*. Water (10 mL) was added to the residue and extracted with EtOAc (3 × 10 mL). The combined organic layer was dried, concentrated *in vacuo* and flash column chromatography (EtOAc:hexane / 1:4) gave *tert*-butyl (8a*S*,12a*R*)-2-[2-(hydroxymethyl)phenyl]-4,5,6,7,8a,9,10,11,12,12a-decahydroazepino[3,2,1-*hi*]pyrido[4,3-*b*]indole-11(8a*H*)-carboxylate (0.043, 84%) as a white solid. MS (ESI): 435 (base, M+H).

10 Step B:

The title compound (0.033 g, 100%) was prepared by the general method of Example 312, step B from *tert*-butyl (8a*S*,12a*R*)-2-[2-(hydroxymethyl)phenyl]-4,5,6,7,8a,9,10,11,12,12a-decahydroazepino[3,2,1-*hi*]pyrido[4,3-*b*]indole-11(8a*H*)-carboxylate (0.043 g, 0.10 mmol) as a white foam. ¹H NMR (CDCl₃, 300 MHz) δ 1.50-1.95 (m, 3H), 1.95-2.10 (m, 3H), 2.44-2.80 (m, 3H), 2.80-3.00 (m, 3H), 3.00-3.10 (m, 1H), 3.10-3.40 (m, 3H), 4.65 (br, 2H), 6.92 (s, 1H), 6.95 (s, 1H), 7.22-7.38 (m, 3H), 7.50-7.57 (m, 1H) ppm. MS (ESI): 335 (base, M+H).

EXAMPLE 342

20 2-[(8a*S*,12a*R*)-4,5,6,7,8a,9,10,11,12,12a-decahydroazepino[3,2,1-*hi*]pyrido[4,3-*b*]indol-2-yl]-5-methoxybenzaldehyde

Step A:

Tert-butyl (8a*S*,12a*R*)-2-(2-formyl-4-methoxyphenyl)-4,5,6,7,8a,9,10,11,12,12a-decahydroazepino[3,2,1-*hi*]pyrido[4,3-*b*]indole-11(8a*H*)-carboxylate (0.094 g, 41%) was prepared by the general method of Example 89, step C from *tert*-butyl (8a*S*,12a*R*)-2-bromo-4,5,6,7,9,10,12,12a-octahydroazepino[3,2,1-*hi*]pyrido[4,3-*b*]indole-11(8a*H*)-carboxylate (0.20 g, 0.50 mmol), 2-formyl-4-methoxyphenylboronic acid (0.18 g, 1.0 mmol), Pd(PPh₃)₂Cl₂ (17 mg, 0.025 mmol), Na₂CO₃ (2.0 M, 1.0 mL, 2.0 mmol) as a white foam. MS (ESI): 463 (base, M+H).

Step B:

The title compound (0.060 g, 81%) was prepared by the general method of Example 312, step B from *tert*-butyl (8a*S*,12a*R*)-2-(2-formyl-4-methoxyphenyl)-4,5,6,7,8a,9,10,11,12,12a-decahydroazepino[3,2,1-*hi*]pyrido[4,3-*b*]indole-11(8a*H*)-carboxylate (0.094 g, 0.20 mmol) as a white foam. ¹H NMR (CDCl₃, 300 MHz) δ 1.50-1.70 (m, 1H), 1.70-1.90 (m, 2H), 1.90-2.10 (m, 4H), 2.50-2.76 (m, 3H), 2.85-3.08 (m, 3H), 3.08-3.20 (m, 1H), 3.25-3.42 (m, 3H), 3.47 (s, 1H), 3.88 (s, 3H), 6.88 (s, 1H), 6.91 (s, 1H), 7.16 (dd, J = 2.6, 8.4 Hz, 1H), 7.35 (d, J = 8.4 Hz, 1H), 7.46 (d, J = 2.6 Hz, 1H), 9.95 (s, 1H) ppm. MS (ESI): 363 (base, M+H).

10

EXAMPLE 343

{2-[(8a*S*,12a*R*)-4,5,6,7,8a,9,10,11,12,12a-decahydroazepino[3,2,1-*hi*]pyrido[4,3-*b*]indol-2-yl]-5-methoxyphenyl}methanol

15 **Step A:**

Tert-butyl (8a*S*,12a*R*)-2-[2-(hydroxymethyl)-4-methoxyphenyl]-4,5,6,7,8a,9,10,11,12,12a-decahydroazepino[3,2,1-*hi*]pyrido[4,3-*b*]indole-11(8a*H*)-carboxylate (0.54 g) was obtained as a byproduct of Example 342 as a white foam. MS (ESI): 465 (base, M+H).

20

Step B:

The title compound (0.42 g, 100%) was prepared by the general method of Example 312, step B from *tert*-butyl (8a*S*,12a*R*)-2-[2-(hydroxymethyl)-4-methoxyphenyl]-4,5,6,7,8a,9,10,11,12,12a-decahydroazepino[3,2,1-*hi*]pyrido[4,3-*b*]indole-11(8a*H*)-carboxylate (0.054 g, 0.12 mmol) as a white foam. ¹H NMR (CDCl₃, 300 MHz) δ 1.50-1.68 (m, 1H), 1.68-2.10 (m, 5H), 2.40-2.80 (m, 3H), 2.80-3.00 (m, 3H), 3.00-3.10 (m, 1H), 3.10-3.40 (m, 3H), 3.86 (s, 3H), 4.62 (br, 2H), 6.78-6.92 (m, 3H), 7.10 (d, J = 3.0 Hz, 1H), 7.19 (d, J = 8.4 Hz, 1H), ppm. MS (ESI): 365 (base, M+H).

30

EXAMPLE 344

4-[(8a*S*,12a*R*)-4,5,6,7,8a,9,10,11,12,12a-decahydroazepino[3,2,1-*hi*]pyrido[4,3-*b*]indol-2-yl]-3-methylbenzonitrile

5 **Step A:**

Tert-butyl (8a*S*,12a*R*)-2-(4-cyano-2-methylphenyl)-4,5,6,7,8a,9,10,11,12,12a-decahydroazepino[3,2,1-*hi*]pyrido[4,3-*b*]indole-11(8a*H*)-carboxylate (0.095 g, 86%) was prepared by the general method of Example 319, step A from *tert-butyl* (8a*S*,12a*R*)-2-bromo-4,5,6,7,9,10,12,12a-octahydroazepino[3,2,1-*hi*]pyrido[4,3-*b*]indole-11(8a*H*)-carboxylate (0.10 g, 0.25 mmol), 4-cyano-2-methylphenylboronic acid (0.080 g, 0.50 mmol), Pd(PPh₃)₄ (12 mg, 0.010 mmol), and Ba(OH)₂ (0.17 M, 3.0 mL, 0.51 mmol) as a white foam. MS (ESI): 444 (base, M+H).

Step B:

15 The title compound (0.074 g, 100%) was prepared by the general method of Example 312, step B from *tert-butyl* (8a*S*,12a*R*)-2-(4-cyano-2-methylphenyl)-4,5,6,7,8a,9,10,11,12,12a-decahydroazepino[3,2,1-*hi*]pyrido[4,3-*b*]indole-11(8a*H*)-carboxylate (0.095 g, 0.21 mmol) as a white foam. ¹H NMR (CDCl₃, 300 MHz) δ 1.50-1.70 (m, 1H), 1.70-2.10 (m, 5H), 2.32 (s, 3H), 2.85-3.00 (m, 3H), 3.08 (dd, J = 6.3, 12.4 Hz, 1H), 3.20-3.50 (m, 4H), 6.85 (s, 2H), 7.29 (d, J = 7.9 Hz, 1H), 7.47 (d, J = 7.9 Hz, 1H), 7.51 (s, 1H) ppm. MS (ESI): 344 (base, M+H).

EXAMPLE 345

25 **1-{2-[(8a*S*,12a*R*)-4,5,6,7,8a,9,10,11,12,12a-decahydroazepino[3,2,1-*hi*]pyrido[4,3-*b*]indol-2-yl]-5-methoxyphenyl}ethanol**

CH₃MgBr (1 M, 2.3 mL, 2.3 mmol) was added to a solution of 2-[(8a*S*,12a*R*)-4,5,6,7,8a,9,10,11,12,12a-decahydroazepino[3,2,1-*hi*]pyrido[4,3-*b*]indol-2-yl]-5-methoxybenzaldehyde (0.080g, 0.23 mmol) in THF (5 mL) at 0°C. The mixture was stirred at room temperature for 18 h and quenched with water (5.0 mL). The mixture was extracted with CH₂Cl₂ (3 × 10 mL) and the organic layer was dried (Na₂SO₄)

and concentrated *in vacuo*. Reverse phase HPLC (H₂O-CH₃CN-TFA (0.05%)) gave the title compound (2.0 mg, 4%). MS (ESI): 379 (base, M+H)

EXAMPLE 346

5 ***tert*-butyl (7a*S*,11a*R*)-2-bromo-5,6,7a,8,9,10,11,11a-octahydro-4*H*-pyrido[3',4':4,5]pyrrolo[3,2,1-*ij*]quinoline-10(7a*H*)-carboxylate**

The title compound (7.73 g, 97%) was prepared by the method of Example 314 from *tert*-butyl (7a*S*,11a*R*)-5,6,7a,8,9,10,11,11a-octahydro-4*H*-pyrido[3',4':4,5]pyrrolo[3,2,1-*ij*]quinoline-10(7a*H*)-carboxylate (6.40 g, 20 mmol) and NBS (3.63 g, 20 mmol) as a white solid.

EXAMPLE 347

15 **(7a*S*,11a*R*)-2-(2,4-dichlorophenyl)-5,6,7a,8,9,10,11,11a-octahydro-4*H*-pyrido[3',4':4,5]pyrrolo[3,2,1-*ij*]quinoline**

Step A:

Tert-butyl (7a*S*,11a*R*)-2-(2,4-dichlorophenyl)-5,6,7a,8,9,10,11,11a-octahydro-4*H*-pyrido[3',4':4,5]pyrrolo[3,2,1-*ij*]quinoline-10(7a*H*)-carboxylate (0.15 g, 63%) was prepared by the method of Example 315 from *tert*-butyl (7a*S*,11a*R*)-2-bromo-5,6,7a,8,9,10,11,11a-octahydro-4*H*-pyrido[3',4':4,5]pyrrolo[3,2,1-*ij*]quinoline-10(7a*H*)-carboxylate (0.20 g, 0.50 mmol), 2,4-dichlorophenylboronic acid (0.19 g, 1.0 mmol), Ba(OH)₂·8H₂O (0.32 g, 1.0 mmol), Pd₂(dba)₃ (7.5 mg, 0.0075 mmol) and PPh₃ (5.24 mg, 0.02 mmol) as a white foam.

Step B:

The title compound (0.087 g, 77%) was prepared by the general method of Example 312, step B from *tert*-butyl (7a*S*,11a*R*)-2-(2,4-dichlorophenyl)-5,6,7a,8,9,10,11,11a-octahydro-4*H*-pyrido[3',4':4,5]pyrrolo[3,2,1-*ij*]quinoline-10(7a*H*)-carboxylate (0.15 g, 0.32 mmol) as a white foam. ¹H NMR (CDCl₃, 300 MHz) δ 1.75-2.00 (m, 2H), 2.08-2.30 (m, 3H), 2.60-2.80 (m, 4H), 2.80-2.92 (m, 2H),

3.07-3.15 (m, 2H), 3.28-3.35 (m, 1H), 3.38-3.48 (m, 1H), (s, 1H), 6.98 (s, 1H), 7.23 (d, J=1.9 Hz, 2H), 7.44 (t, J=1.3 Hz, 1H) ppm.

EXAMPLE 348

5 (7a*S*,11a*R*)-2-(3,4-dichlorophenyl)-5,6,7a,8,9,10,11,11a-octahydro-4*H*-pyrido[3',4':4,5]pyrrolo[3,2,1-*ij*]quinoline

Step A:

Tert-butyl (7a*S*,11a*R*)-2-(3,4-dichlorophenyl)-5,6,7a,8,9,10,11,11a-octahydro-4*H*-pyrido[3',4':4,5]pyrrolo[3,2,1-*ij*]quinoline-10(7a*H*)-carboxylate (0.085 g, 37%) was prepared by the general method of Example 89, step C from *tert*-butyl (7a*S*,11a*R*)-2-bromo-5,6,7a,8,9,10,11,11a-octahydro-4*H*-pyrido[3',4':4,5]pyrrolo[3,2,1-*ij*]quinoline-10(7a*H*)-carboxylate (0.20 g, 0.50 mmol), 3,4-dichlorophenylboronic acid (0.19 g, 1.0 mmol), Pd(PPh₃)₂Cl₂ (17 mg, 0.025 mmol), Na₂CO₃ (2.0 M, 1.0 mL, 2.0 mmol) as a white foam. MS (ESI): 459 (base, M+H).

Step B:

The title compound (0.066 g, 100%) was prepared by the general method of Example 312, step B from *tert*-butyl (7a*S*,11a*R*)-2-(3,4-dichlorophenyl)-5,6,7a,8,9,10,11,11a-octahydro-4*H*-pyrido[3',4':4,5]pyrrolo[3,2,1-*ij*]quinoline-10(7a*H*)-carboxylate (0.085 g, 0.19 mmol) as a white foam. ¹H NMR (CDCl₃, 300 MHz) δ 1.80-2.05 (m, 2H), 2.05-2.20 (m, 2H), 2.55-2.80 (m, 4H), 2.82-2.98 (m, 2H), 3.07-3.20 (m, 2H), 3.20-3.38 (m, 1H), 3.38-3.48 (m, 1H), 3.64 (br, 1H), 7.01 (s, 1H), 7.11 (s, 1H), 7.34 (dd, J = 1.8, 8.4 Hz, 1H), 7.43 (d, J = 8.4 Hz, 2H), 7.59 (d, J = 1.8 Hz, 1H) ppm. MS (ESI): 359 (base, M+H).

EXAMPLE 349

(7a*S*,11a*R*)-2-(3,5-dichlorophenyl)-5,6,7a,8,9,10,11,11a-octahydro-4*H*-pyrido[3',4':4,5]pyrrolo[3,2,1-*ij*]quinoline

5 **Step A:**

Tert-butyl (7a*S*,11a*R*)-2-(3,5-dichlorophenyl)-5,6,7a,8,9,10,11,11a-octahydro-4*H*-pyrido[3',4':4,5]pyrrolo[3,2,1-*ij*]quinoline-10(7a*H*)-carboxylate (0.045 g, 40%) was prepared by the general method of Example 89, step C from *tert*-butyl (7a*S*,11a*R*)-2-bromo-5,6,7a,8,9,10,11,11a-octahydro-4*H*-pyrido[3',4':4,5]pyrrolo[3,2,1-*ij*]quinoline-10(7a*H*)-carboxylate (0.098 g, 0.25 mmol), 3,5-dichlorophenylboronic acid (0.10 g, 0.5 mmol), Pd(PPh₃)₂Cl₂ (8.8 mg, 0.013 mmol), Na₂CO₃ (2.0 M, 0.5 mL, 1.0 mmol) as a white foam. MS (ESI): 459 (base, M+H).

15 **Step B:**

The title compound (0.035 g, 100%) was prepared by the general method of Example 312, step B from *tert*-butyl (7a*S*,11a*R*)-2-(3,5-dichlorophenyl)-5,6,7a,8,9,10,11,11a-octahydro-4*H*-pyrido[3',4':4,5]pyrrolo[3,2,1-*ij*]quinoline-10(7a*H*)-carboxylate (0.045 g, 0.10 mmol) as a white foam. ¹H NMR (CDCl₃, 300 MHz) δ 1.80-2.05 (m, 2H), 2.05-2.20 (m, 2H), 2.55-2.80 (m, 4H), 2.88-2.96 (m, 3H), 3.07-3.20 (m, 2H), 3.23-3.36 (m, 1H), 3.38-3.48 (m, 1H), 7.08 (s, 1H), 7.10 (s, 1H), 7.21 (t, J=1.9 Hz, 1H), 7.37 (d, J=1.9 Hz, 2H) ppm. MS (ESI): 359 (base, M+H).

EXAMPLE 350

(7a*S*,11a*R*)-2-(2,5-dichlorophenyl)-5,6,7a,8,9,10,11,11a-octahydro-4*H*-pyrido[3',4':4,5]pyrrolo[3,2,1-*ij*]quinoline

Step A:

Tert-butyl (7a*S*,11a*R*)-2-(2,5-dichlorophenyl)-5,6,7a,8,9,10,11,11a-octahydro-4*H*-pyrido[3',4':4,5]pyrrolo[3,2,1-*ij*]quinoline-10(7a*H*)-carboxylate (0.080 g, 55%) was prepared by the general method of Example 319, step A from *tert*-butyl

(7a*S*,11a*R*)-2-bromo-5,6,7a,8,9,10,11,11a-octahydro-4*H*-pyrido[3',4':4,5]pyrrolo[3,2,1-*ij*]quinoline-10(7a*H*)-carboxylate (0.13 g, 0.32 mmol), 2,5-dichlorophenylboronic acid (0.12 g, 0.64 mmol), Pd(PPh₃)₄ (14 mg, 0.012 mmol), and Ba(OH)₂ (0.17 M, 3.0 mL, 0.51 mmol) as a white foam. MS (ESI): 459 (base, M+H).

Step B:

The title compound (0.063 g, 100%) was prepared by the general method of Example 312, step B from *tert*-butyl (7a*S*,11a*R*)-2-(2,5-dichlorophenyl)-5,6,7a,8,9,10,11,11a-octahydro-4*H*-pyrido[3',4':4,5]pyrrolo[3,2,1-*ij*]quinoline-10(7a*H*)-carboxylate (0.080 g, 0.17 mmol) as a white foam. ¹H NMR (CDCl₃, 300 MHz) δ 1.80-2.05 (m, 2H), 2.05-2.20 (m, 2H), 2.55-2.80 (m, 4H), 2.88-2.96 (m, 3H), 3.07-3.20 (m, 2H), 3.23-3.36 (m, 1H), 3.38-3.48 (m, 1H), 6.95 (s, 1H), 6.99 (s, 1H), 7.16 (dd, J=2.7, 8.4 Hz, 1H), 7.30 (d, J=2.7 Hz, 1H), 7.34 (d, J=8.4 Hz) ppm. MS (ESI): 359 (base, M+H).

EXAMPLE 351

(7a*S*,11a*R*)-2-(2,6-dichlorophenyl)-5,6,7a,8,9,10,11,11a-octahydro-4*H*-pyrido[3',4':4,5]pyrrolo[3,2,1-*ij*]quinoline

Step A:

Tert-butyl (7a*S*,11a*R*)-2-(2,6-dichlorophenyl)-5,6,7a,8,9,10,11,11a-octahydro-4*H*-pyrido[3',4':4,5]pyrrolo[3,2,1-*ij*]quinoline-10(7a*H*)-carboxylate (0.023 g, 19%) was prepared by the general method of Example 320, step A from *tert*-butyl (8a*S*,11a*R*)-2-bromo-4,5,6,7,9,10,12,12a-octahydroazepino[3,2,1-*hi*]pyrido[4,3-*b*]indole-11(8a*H*)-carboxylate (0.10 g, 0.26 mmol), 2,6-dichlorophenyl boronic acid (0.10 g, 0.52 mmol), Pd(dppf)₂Cl₂ (10 mg, 0.012 mmol), TEA (1.0 mL, 7.2 mmol) as a white foam.

Step B:

The title compound (0.018 g, 100%) was prepared by the general method of Example 312, step B from *tert*-butyl (7a*S*,11a*R*)-2-(2,6-dichlorophenyl)-5,6,7a,8,9,10,11,11a-octahydro-4*H*-pyrido[3',4':4,5]pyrrolo[3,2,1-*ij*]quinoline-10(7a*H*)-carboxylate (0.023 g, 0.050 mmol) as a white foam. ¹H NMR (CDCl₃, 300 MHz) δ 1.80-2.05 (m, 2H), 2.05-2.20 (m, 2H), 2.55-2.80 (m, 4H), 2.88-2.96 (m, 3H), 3.07-3.20 (m, 2H), 3.23-3.36 (m, 1H), 3.38-3.48 (m, 1H), 6.73 (s, 1H), 6.79 (s, 1H), 7.16 (t, J=8.0 Hz, 1H), 7.38 (d, J=8.0 Hz) ppm. MS (ESI): 359 (base, M+H).

10

EXAMPLE 352

(7a*S*,11a*R*)-2-(2-chlorophenyl)-5,6,7a,8,9,10,11,11a-octahydro-4*H*-pyrido[3',4':4,5]pyrrolo[3,2,1-*ij*]quinoline

Step A:

Tert-butyl (7a*S*,11a*R*)-2-(2-chlorophenyl)-5,6,7a,8,9,10,11,11a-octahydro-4*H*-pyrido[3',4':4,5]pyrrolo[3,2,1-*ij*]quinoline-10(7a*H*)-carboxylate (0.054 g, 51%) was prepared by the general method of Example 89, step C from *tert*-butyl (7a*S*,11a*R*)-2-bromo-5,6,7a,8,9,10,11,11a-octahydro-4*H*-pyrido[3',4':4,5]pyrrolo[3,2,1-*ij*]quinoline-10(7a*H*)-carboxylate (0.098 g, 0.25 mmol), 2-chlorophenylboronic acid (0.078 g, 0.5 mmol), Pd(PPh₃)₂Cl₂ (8.8 mg, 0.013 mmol), Na₂CO₃ (2.0 M, 0.5 mL, 1.0 mmol) as a white foam. MS (ESI): 425 (base, M+H).

20

Step B:

The title compound (0.040 g, 99%) was prepared by the general method of Example 312, step B from *tert*-butyl (7a*S*,11a*R*)-2-(2-chlorophenyl)-5,6,7a,8,9,10,11,11a-octahydro-4*H*-pyrido[3',4':4,5]pyrrolo[3,2,1-*ij*]quinoline-10(7a*H*)-carboxylate (0.054 g, 0.13 mmol) as a white foam. ¹H NMR (CDCl₃, 300 MHz) δ 1.80-2.05 (m, 2H), 2.05-2.20 (m, 2H), 2.55-2.80 (m, 4H), 2.88-2.96 (m, 3H), 3.07-3.20 (m, 2H), 3.23-3.36 (m, 1H), 3.38-3.48 (m, 1H), 6.97 (s, 1H), 7.02 (s, 1H), 7.12-7.35 (m, 3H), 7.35-7.46 (m, 2H) ppm. MS (ESI): 325 (base, M+H).

25

30

EXAMPLE 353

(7a*S*,11a*R*)-2-(3-chlorophenyl)-5,6,7a,8,9,10,11,11a-octahydro-4*H*-pyrido[3',4':4,5]pyrrolo[3,2,1-*ij*]quinoline5 **Step A:**

Tert-butyl (7a*S*,11a*R*)-2-(3-chlorophenyl)-5,6,7a,8,9,10,11,11a-octahydro-4*H*-pyrido[3',4':4,5]pyrrolo[3,2,1-*ij*]quinoline-10(7a*H*)-carboxylate (0.060 g, 57%) was prepared by the general method of Example 89, step C from *tert*-butyl (7a*S*,11a*R*)-2-bromo-5,6,7a,8,9,10,11,11a-octahydro-4*H*-pyrido[3',4':4,5]pyrrolo[3,2,1-*ij*]quinoline-10(7a*H*)-carboxylate (0.098 g, 0.25 mmol), 3-chlorophenylboronic acid (0.078 g, 0.5 mmol), Pd(PPh₃)₂Cl₂ (8.8 mg, 0.013 mmol), Na₂CO₃ (2.0 M, 0.5 mL, 1.0 mmol) as a white foam. MS (ESI): 425 (base, M+H).

Step B:

15 The title compound (0.046 g, 100%) was prepared by the general method of Example 312, step B from *tert*-butyl (7a*S*,11a*R*)-2-(3-chlorophenyl)-5,6,7a,8,9,10,11,11a-octahydro-4*H*-pyrido[3',4':4,5]pyrrolo[3,2,1-*ij*]quinoline-10(7a*H*)-carboxylate (0.060 g, 0.14 mmol) as a white foam. ¹H NMR (CDCl₃, 300 MHz) δ 1.80-2.05 (m, 2H), 2.05-2.20 (m, 2H), 2.55-2.80 (m, 4H), 2.88-2.96 (m, 3H), 20 3.07-3.20 (m, 2H), 3.23-3.36 (m, 1H), 3.38-3.48 (m, 1H), 7.11 (s, 1H), 7.12 (s, 1H), 7.20-7.40 (m, 3H), 7.48 (t, J=1.7 Hz, 1H) ppm. MS (ESI): 325 (base, M+H).

EXAMPLE 354

(7a*S*,11a*R*)-2-(4-chlorophenyl)-5,6,7a,8,9,10,11,11a-octahydro-4*H*-pyrido[3',4':4,5]pyrrolo[3,2,1-*ij*]quinoline

25

Step A:

Tert-butyl (7a*S*,11a*R*)-2-(4-chlorophenyl)-5,6,7a,8,9,10,11,11a-octahydro-4*H*-pyrido[3',4':4,5]pyrrolo[3,2,1-*ij*]quinoline-10(7a*H*)-carboxylate (0.045 g, 21%) was prepared by the general method of Example 89, step C from *tert*-butyl (7a*S*,11a*R*)-2-bromo-5,6,7a,8,9,10,11,11a-octahydro-4*H*-pyrido[3',4':4,5]pyrrolo[3,2,1-*ij*]quinoline-

10(7aH)-carboxylate (0.20 g, 0.50 mmol), 4-chlorophenylboronic acid (0.16 g, 1.0 mmol), Pd(PPh₃)₂Cl₂ (17 mg, 0.025 mmol), Na₂CO₃ (2.0 M, 1.0 mL, 2.0 mmol) as a white foam. MS (ESI): 425 (base, M+H).

5 Step B:

The title compound (0.033 g, 99%) was prepared by the general method of Example 312, step B from *tert*-butyl (7aS,11aR)-2-(4-chlorophenyl)-5,6,7a,8,9,10,11,11a-octahydro-4H-pyrido[3',4':4,5]pyrrolo[3,2,1-*ij*]quinoline-10(7aH)-carboxylate (0.045 g, 0.11 mmol) as a white foam. ¹H NMR (CDCl₃, 300 MHz) δ 1.80-2.05 (m, 2H), 2.05-2.20 (m, 2H), 2.58-2.82 (m, 4H), 2.82-3.06 (m, 3H), 3.07-3.20 (m, 2H), 3.23-3.40 (m, 1H), 3.40-3.48 (m, 1H), 7.11 (s, 1H), 7.13 (s, 1H), 7.34 (d, J=8.4 Hz, 2H), 7.45 (d, J=8.4 Hz) ppm. MS (ESI): 325 (base, M+H).

EXAMPLE 355

15 (7aS,11aR)-2-(2,6-difluorophenyl)-5,6,7a,8,9,10,11,11a-octahydro-4H-pyrido[3',4':4,5]pyrrolo[3,2,1-*ij*]quinoline

Step A:

Tert-butyl (7aS,11aR)-2-(2,6-difluorophenyl)-5,6,7a,8,9,10,11,11a-octahydro-4H-pyrido[3',4':4,5]pyrrolo[3,2,1-*ij*]quinoline-10(7aH)-carboxylate (0.064 g, 15%) was prepared by the general method of Example 320, step A from *tert*-butyl (8aS,11aR)-2-bromo-4,5,6,7,9,10,12,12a-octahydroazepino[3,2,1-*hi*]pyrido[4,3-*b*]indole-11(8aH)-carboxylate (0.39 g, 1.0 mmol), 2,6-difluorophenylboronic acid (0.63 g, 4.0 mmol), Pd(dppf)₂Cl₂ (48 mg, 0.06 mmol), TEA (3.0 mL, 22 mmol) as a white foam.

Step B:

The title compound (0.029 g, 59%) was prepared by the general method of Example 312, step B from *tert*-butyl (7aS,11aR)-2-(2,6-difluorophenyl)-5,6,7a,8,9,10,11,11a-octahydro-4H-pyrido[3',4':4,5]pyrrolo[3,2,1-*ij*]quinoline-10(7aH)-carboxylate (0.064 g, 0.15 mmol) as a white foam. ¹H NMR (CDCl₃, 300

MHz) δ 1.80-2.05 (m, 2H), 2.05-2.25 (m, 2H), 2.58-2.83 (m, 4H), 2.83-3.08 (m, 2H), 3.08-3.60 (m, 5H), 6.85-7.08 (m, 4H), 7.08-7.22 (m, 1H) ppm.

EXAMPLE 356

5 (7a*S*,11a*R*)-2-(2,6-difluorophenyl)-10-methyl-5,6,7a,8,9,10,11,11a-octahydro-4*H*-pyrido[3',4':4,5]pyrrolo[3,2,1-*ij*]quinoline

A mixture of (7a*S*,11a*R*)-2-(2,6-difluorophenyl)-5,6,7a,8,9,10,11,11a-octahydro-4*H*-pyrido[3',4':4,5]pyrrolo[3,2,1-*ij*]quinoline (0.050, 0.15 mmol), HCHO
 10 (0.20 mL, 2.9 mmol) and formic acid (1.0 mL, 2.9 mmol) was heated at 80 °C for 4 h and cooled to room temperature. Water (5.0 mL) was added and the solution was basified with saturated Na₂CO₃ until pH > 8. The mixture was extracted with CH₂Cl₂ (3 × 10 mL), dried (Na₂SO₄) and flash column chromatography (1-5% MeOH in CHCl₃) gave the title compound (0.032 g, 62%) as a white foam. ¹H NMR (CDCl₃,
 15 300 MHz) δ 2.00-2.20 (m, 5H), 2.20-2.50 (m, 4H), 2.55-2.68 (m, 1H), 2.68-2.82 (m, 3H), 2.86-2.98 (m, 1H), 3.28-3.42 (m, 3H), 6.90-7.08 (m, 4H), 7.14-7.25 (m, 1H) ppm. MS (ESI): 341 (base, M+H).

EXAMPLE 357

20 (7a*S*,11a*R*)-2-(2,3-difluorophenyl)-5,6,7a,8,9,10,11,11a-octahydro-4*H*-pyrido[3',4':4,5]pyrrolo[3,2,1-*ij*]quinoline

Step A:

Tert-butyl (7a*S*,11a*R*)-2-(2,3-difluorophenyl)-5,6,7a,8,9,10,11,11a-octahydro-
 25 4*H*-pyrido[3',4':4,5]pyrrolo[3,2,1-*ij*]quinoline-10(7a*H*)-carboxylate (0.15 g, 70%) was prepared by the general method of Example 89, step C from *tert*-butyl (7a*S*,11a*R*)-2-bromo-5,6,7a,8,9,10,11,11a-octahydro-4*H*-pyrido[3',4':4,5]pyrrolo[3,2,1-*ij*]quinoline-10(7a*H*)-carboxylate (0.20 g, 0.50 mmol), 2,3-difluorophenyl boronic acid (0.16 g, 1.0 mmol), Pd(PPh₃)₂Cl₂ (17 mg, 0.025
 30 mmol), Na₂CO₃ (2.0 M, 1.0 mL, 2.0 mmol) as a white foam. MS (ESI): 427 (base, M+H).

Step B:

The title compound (0.10 g, 88%) was prepared by the general method of Example 312, step B from *tert*-butyl (7a*S*,11a*R*)-2-(2,3-difluorophenyl)-5,6,7a,8,9,10,11,11a-octahydro-4*H*-pyrido[3',4':4,5]pyrrolo[3,2,1-*ij*]quinoline-10(7a*H*)-carboxylate (0.15 g, 0.35 mmol) as a white foam. ¹H NMR (CDCl₃, 300 MHz) δ 1.75-2.00 (m, 2H), 2.05-2.30 (m, 3H), 2.60-2.80 (m, 4H), 2.80-2.90 (m, 2H), 3.02-3.16 (m, 2H), 3.24-3.38 (m, 1H), 3.38-3.48 (m, 1H), 6.94-7.20 (m, 5H) ppm. MS (ESI): 327 (base, M+H).

EXAMPLE 358

(7a*S*,11a*R*)-2-(3,4-difluorophenyl)-5,6,7a,8,9,10,11,11a-octahydro-4*H*-pyrido[3',4':4,5]pyrrolo[3,2,1-*ij*]quinoline

Step A:

Tert-butyl (7a*S*,11a*R*)-2-(3,4-difluorophenyl)-5,6,7a,8,9,10,11,11a-octahydro-4*H*-pyrido[3',4':4,5]pyrrolo[3,2,1-*ij*]quinoline-10(7a*H*)-carboxylate (0.077 g, 72%) was prepared by the general method of Example 319, step A from *tert*-butyl (7a*S*,11a*R*)-2-bromo-5,6,7a,8,9,10,11,11a-octahydro-4*H*-pyrido[3',4':4,5]pyrrolo[3,2,1-*ij*]quinoline-10(7a*H*)-carboxylate (0.10 g, 0.25 mmol), 3,4-difluorophenyl boronic acid (0.080 g, 0.50 mmol), Pd(PPh₃)₄ (12 mg, 0.010 mmol), and Ba(OH)₂ (0.17 M, 3.0 mL, 0.51 mmol) as a white foam. MS (ESI): 427 (base, M+H).

Step B:

The title compound (0.054 g, 90%) was prepared by the general method of Example 312, step B from *tert*-butyl (7a*S*,11a*R*)-2-(3,4-difluorophenyl)-5,6,7a,8,9,10,11,11a-octahydro-4*H*-pyrido[3',4':4,5]pyrrolo[3,2,1-*ij*]quinoline-10(7a*H*)-carboxylate (0.077 g, 0.18 mmol) as a white foam. ¹H NMR (CDCl₃, 300 MHz) δ 1.70-2.00 (m, 4H), 2.10-2.50 (m, 3H), 2.50-2.70 (m, 1H), 2.79-2.85 (m, 2H), 3.10-3.60 (m, 5H), 7.06-7.35(m, 5H) ppm. MS (ESI): 327 (base, M+H).

EXAMPLE 359

(7a*S*,11a*R*)-2-(3-fluorophenyl)-5,6,7a,8,9,10,11,11a-octahydro-4*H*-
pyrido[3',4':4,5]pyrrolo[3,2,1-*ij*]quinoline

5

Step A:

Tert-butyl (7a*S*,11a*R*)-2-(3-fluorophenyl)-5,6,7a,8,9,10,11,11a-octahydro-4*H*-
pyrido[3',4':4,5]pyrrolo[3,2,1-*ij*]quinoline-10(7a*H*)-carboxylate (0.055 g, 52%) was
prepared by the general method of Example 319, step A from *tert*-butyl (7a*S*,11a*R*)-2-
10 bromo-5,6,7a,8,9,10,11,11a-octahydro-4*H*-pyrido[3',4':4,5]pyrrolo[3,2,1-*ij*]quinoline-
10(7a*H*)-carboxylate (0.10 g, 0.25 mmol), 3-fluorophenyl boronic acid (0.070 g, 0.50
mmol), Pd(PPh₃)₄ (12 mg, 0.010 mmol), and Ba(OH)₂ (0.17 M, 3.0 mL, 0.51 mmol)
as a white foam. MS (ESI): 409 (base, M+H).

15 Step B:

The title compound (0.042 g, 100%) was prepared by the general method of
Example 312, step B from *tert*-butyl (7a*S*,11a*R*)-2-(3-fluorophenyl)-
5,6,7a,8,9,10,11,11a-octahydro-4*H*-pyrido[3',4':4,5]pyrrolo[3,2,1-*ij*]quinoline-
10(7a*H*)-carboxylate (0.055 g, 0.13 mmol) as a white foam. ¹H NMR (CDCl₃, 300
20 MHz) δ 2.05-2.22 (m, 4H), 2.55-2.68 (m, 1H), 2.68-2.80 (m, 3H), 3.00-3.20 (m, 2H),
3.2-3.48 (m, 4H), 5.00-5.50 (br, 1H), 6.85-7.00 (m, 1H), 7.08-7.40 (m, 5H) ppm. MS
(ESI): 309 (base, M+H).

EXAMPLE 360

25 (7a*S*,11a*R*)-2-[2-chloro-4-methoxyphenyl]-5,6,7a,8,9,10,11,11a-octahydro-4*H*-
pyrido[3',4':4,5]pyrrolo[3,2,1-*ij*]quinoline

Step A:

Tert-butyl (7a*S*,11a*R*)-2-[2-chloro-4-methoxyphenyl]-5,6,7a,8,9,10,11,11a-
30 octahydro-4*H*-pyrido[3',4':4,5]pyrrolo[3,2,1-*ij*]quinoline-10(7a*H*)-carboxylate (0.053
g, 23%) was prepared by the general method of Example 89, step C from *tert*-butyl

(7a*S*,11a*R*)-2-bromo-5,6,7a,8,9,10,11,11a-octahydro-4*H*-pyrido[3',4':4,5]pyrrolo[3,2,1-*ij*]quinoline-10(7a*H*)-carboxylate (0.20 g, 0.50 mmol), 2-chloro-4-methoxyphenyl boronic acid (0.19 g, 1.0 mmol), Pd(PPh₃)₂Cl₂ (17 mg, 0.025 mmol), Na₂CO₃ (2.0 M, 1.0 mL, 2.0 mmol) as a white foam.

5

Step B:

The title compound (0.035 g, 85%) was prepared by the general method of Example 312, step B from *tert*-butyl (7a*S*,11a*R*)-2-[2-chloro-4-methoxyphenyl]-5,6,7a,8,9,10,11,11a-octahydro-4*H*-pyrido[3',4':4,5]pyrrolo[3,2,1-*ij*]quinoline-10(7a*H*)-carboxylate (0.053 g, 0.12 mmol) as a white foam. ¹H NMR (CDCl₃, 300 MHz) δ 1.80-2.05 (m, 2H), 2.05-2.20 (m, 3H), 2.58-2.68 (m, 1H), 2.68-2.80 (m, 2H), 2.85-3.05 (m, 3H), 3.07-3.20 (m, 2H), 3.23-3.36 (m, 1H), 3.38-3.48 (m, 1H), 6.95 (s, 1H), 6.99 (s, 1H), 7.16 (dd, J=2.7, 8.4 Hz, 1H), 7.30 (d, J=2.7 Hz, 1H), 7.34 (d, J=8.4 Hz, 1H) ppm.

15

EXAMPLE 361

(7a*S*,11a*R*)-2-[2-fluoro-4-methoxyphenyl]-5,6,7a,8,9,10,11,11a-octahydro-4*H*-pyrido[3',4':4,5]pyrrolo[3,2,1-*ij*]quinoline

20 **Step A:**

Tert-butyl (7a*S*,11a*R*)-2-[2-fluoro-4-methoxyphenyl]-5,6,7a,8,9,10,11,11a-octahydro-4*H*-pyrido[3',4':4,5]pyrrolo[3,2,1-*ij*]quinoline-10(7a*H*)-carboxylate (0.15 g, 68%) was prepared by the general method of Example 89, step C from *tert*-butyl (7a*S*,11a*R*)-2-bromo-5,6,7a,8,9,10,11,11a-octahydro-4*H*-pyrido[3',4':4,5]pyrrolo[3,2,1-*ij*]quinoline-10(7a*H*)-carboxylate (0.20 g, 0.50 mmol), 2-fluoro-4-methoxyphenylboronic acid (0.17 g, 1.0 mmol), Pd(PPh₃)₂Cl₂ (17 mg, 0.025 mmol), Na₂CO₃ (2.0 M, 1.0 mL, 2.0 mmol) as a white foam. MS (ESI): 339 (base, M+H).

25

Step B:

The title compound (0.11 g, 94%) was prepared by the general method of Example 312, step B from *tert*-butyl (7a*S*,11a*R*)-2-[2-fluoro-4-methoxyphenyl]-5,6,7a,8,9,10,11,11a-octahydro-4*H*-pyrido[3',4':4,5]pyrrolo[3,2,1-*ij*]quinoline-

10(7a*H*)-carboxylate (0.15 g, 0.34 mmol) as a white foam. ¹H NMR (CDCl₃, 300 MHz) δ 1.70-1.88 (m, 1H), 1.88-2.00 (m, 1H), 2.00-2.20 (m, 3H), 2.55-2.80 (m, 4H), 2.80-2.96 (m, 2H), 3.02-3.12 (m, 2H), 3.28-3.37 (m, 1H), 3.38-3.48 (m, 1H), 3.81 (s, 3H), 6.64-6.75 (m, 2H), 7.03 (s, 1H), 7.07 (s, 1H), 7.29 (t, J=8.8 Hz, 1H) ppm. MS (ESI): 339 (base, M+H).

10

EXAMPLE 362

(7a*S*,11a*R*)-2-(4-methoxy-2-methylphenyl)-5,6,7a,8,9,10,11,11a-octahydro-4*H*-pyrido[3',4':4,5]pyrrolo[3,2,1-*ij*]quinoline

15 **Step A:**

Tert-butyl (7a*S*,11a*R*)-2-(4-methoxy-2-methylphenyl)-5,6,7a,8,9,10,11,11a-octahydro-4*H*-pyrido[3',4':4,5]pyrrolo[3,2,1-*ij*]quinoline-10(7a*H*)-carboxylate (0.15 g, 68%) was prepared by the general method of Example 89, step C from *tert*-butyl (7a*S*,11a*R*)-2-bromo-5,6,7a,8,9,10,11,11a-octahydro-4*H*-

20 pyrido[3',4':4,5]pyrrolo[3,2,1-*ij*]quinoline-10(7a*H*)-carboxylate (0.20 g, 0.50 mmol), 4-methoxy-2-methylphenylboronic acid (0.17 g, 1.0 mmol), Pd(PPh₃)₂Cl₂ (17 mg, 0.025 mmol), Na₂CO₃ (2.0 M, 1.0 mL, 2.0 mmol) as a white foam. MS (ESI): 449 (base, M+H).

25 **Step B:**

The title compound (0.095 g, 97%) was prepared by the general method of Example 312, step B from *tert*-butyl (7a*S*,11a*R*)-2-(4-methoxy-2-methylphenyl)-5,6,7a,8,9,10,11,11a-octahydro-4*H*-pyrido[3',4':4,5]pyrrolo[3,2,1-*ij*]quinoline-10(7a*H*)-carboxylate (0.13 g, 0.29 mmol) as a white foam. ¹H NMR (CDCl₃, 300

30 MHz) δ 1.74-1.88 (m, 1H), 1.88-2.00 (m, 1H), 2.05-2.28 (m, 3H), 2.28 (s, 3H), 2.55-2.80 (m, 4H), 2.80-2.92 (m, 2H), 3.00-3.12 (m, 2H), 3.28-3.36 (m, 1H), 3.36-3.45 (m,

1H), 3.82 (s, 3H), 6.70-6.82 (m, 3H), 6.84 (s, 1H), 7.14 (d, J=8.4 Hz, 1H) ppm. MS (ESI): 349 (base, M+H).

EXAMPLE 363

5 **(7aS,11aR)-2-[4-methoxy-2-(trifluoromethyl)phenyl]-5,6,7a,8,9,10,11,11a-octahydro-4H-pyrido[3',4':4,5]pyrrolo[3,2,1-ij]quinoline**

Step A:

Tert-butyl (7aS,11aR)-2-[4-methoxy-2-(trifluoromethyl)phenyl]-
 10 5,6,7a,8,9,10,11,11a-octahydro-4H-pyrido[3',4':4,5]pyrrolo[3,2,1-ij]quinoline-
 10(7aH)-carboxylate (3.02 g, 61%) was prepared by the general method of Example
 89, step C from *tert-butyl* (7aS,11aR)-2-bromo-5,6,7a,8,9,10,11,11a-octahydro-4H-
 pyrido[3',4':4,5]pyrrolo[3,2,1-ij]quinoline-10(7aH)-carboxylate (3.93 g, 10 mmol), 4-
 methoxy-2-(trifluoromethyl)phenylboronic acid (4.40 g, 20 mmol), Pd(PPh₃)₂Cl₂
 15 (0.35 g, 0.50 mmol), Na₂CO₃ (2.0 M, 20 mL, 40 mmol) as a white solid. MS (ESI):
 489 (base, M+H).

Step B:

The title compound (2.38 g, 99%) was prepared by the general method of
 20 Example 312, step B from *tert-butyl* (7aS,11aR)-2-[4-methoxy-2-
 (trifluoromethyl)phenyl]-5,6,7a,8,9,10,11,11a-octahydro-4H-
 pyrido[3',4':4,5]pyrrolo[3,2,1-ij]quinoline-10(7aH)-carboxylate (3.02 g, 6.1 mmol) as
 a white foam. ¹H NMR (CDCl₃, 300 MHz) δ 1.80-2.05 (m, 2H), 2.08-2.10 (m, 3H),
 2.60-2.80 (m, 4H), 2.80-2.96 (m, 2H), 3.04-3.15 (m, 2H), 3.32 (td, J=4.0, 10.0 Hz,
 25 1H), 3.40-3.48 (m, 1H), 3.88 (s, 3H), 6.81 (s, 1H), 6.85 (s, 1H), 7.04 (dd, J=2.7, 8.4
 Hz, 1H), 7.20-7.28 (m, 2H) ppm. MS (ESI): 389 (base, M+H).

EXAMPLE 364

2-[4-methoxy-2-(trifluoromethyl)phenyl]-5,6,8,9,10,11-hexahydro-4*H*-pyrido[3',4':4,5]pyrrolo[3,2,1-*ij*]quinoline

5 **Step A:**

Tert-butyl 2-[4-methoxy-2-(trifluoromethyl)phenyl]-5,6,8,9,10,11-hexahydro-4*H*-pyrido[3',4':4,5]pyrrolo[3,2,1-*ij*]quinoline-10 (7*aH*)-carboxylate (0.78 g) was obtained as a byproduct of Example 363 as a white solid.

10 **Step B:**

The title compound (0.60 g, 98%) was prepared by the general method of Example 312, step B from *tert-butyl* 2-[4-methoxy-2-(trifluoromethyl)phenyl]-5,6,8,9,10,11-hexahydro-4*H*-pyrido[3',4':4,5]pyrrolo[3,2,1-*ij*]quinoline-10(7*aH*)-carboxylate (0.78 g, 1.6 mmol) as a white foam. ¹H NMR (CDCl₃, 300 MHz) δ 2.20-2.30 (m, 2H), 2.79 (t, J=5.4 Hz, 2H), 2.90-3.20 (m, 3H), 3.30 (t, J=5.8 Hz, 2H), 3.91 (s, 3H), 3.98 (t, J=5.8 Hz, 2H), 4.12 (s, 2H), 6.84 (s, 1H), 7.07 (dd, J=2.5, 8.4 Hz, 1H), 7.18 (s, 1H), 7.25-7.35 (m, 2H) ppm. MS (ESI): 428 (base, M+CH₃CN).

EXAMPLE 365

4-[(7*aS*,11*aR*)-5,6,7*a*,8,9,10,11,11*a*-octahydro-4*H*-pyrido[3',4':4,5]pyrrolo[3,2,1-*ij*]quinolin-2-yl]-3-(trifluoromethyl)phenol

BBr₃ in CH₂Cl₂ (0.91 M, 0.66 mL, 0.60 mmol) was added dropwise to a solution of *tert-butyl* (7*aS*,11*aR*)-2-[4-methoxy-2-(trifluoromethyl)phenyl]-5,6,7*a*,8,9,10,11,11*a*-octahydro-4*H*-pyrido[3',4':4,5]pyrrolo[3,2,1-*ij*]quinoline-10(7*aH*)-carboxylate (0.049 g, 0.10 mmol) in CH₂Cl₂ (5.0 mL) at room temperature under N₂. The mixture was stirred for 18 h before quenched with water (5.0 mL). The mixture was basified with saturated NaHCO₃ until pH ~ 8 and extracted with CH₂Cl₂ (3 × 10 mL). The combined organic layer was dried (Na₂SO₄) and concentrated *in vacuo*. Reverse phase HPLC (H₂O-CH₃CN-TFA (0.05%)) gave the title compound (0.012 g, 32%) as a white solid. ¹H NMR (CDCl₃, 300 MHz) δ 2.00-

2.22 (m, 2H), 2.05-2.20 (m, 2H), 2.55-2.80 (m, 4H), 2.88-2.96 (m, 2H), 3.07-3.20 (m, 2H), 3.23-3.36 (m, 1H), 3.38-3.48 (m, 1H), 6.95 (s, 1H), 6.99 (s, 1H), 7.16 (dd, J=2.7, 8.4 Hz, 1H), 7.30 (d, J=2.7 Hz, 1H), 7.34 (d, J=8.4 Hz) ppm. MS (ESI): 375 (base, M+H).

5

EXAMPLE 366

(7a*S*,11a*R*)-2-[2-(trifluoromethyl)phenyl]-5,6,7a,8,9,10,11,11a-octahydro-4*H*-pyrido[3',4':4,5]pyrrolo[3,2,1-*ij*]quinoline

10 Step A:

Tert-butyl (7a*S*,11a*R*)-2-[2-(trifluoromethyl)phenyl]-5,6,7a,8,9,10,11,11a-octahydro-4*H*-pyrido[3',4':4,5]pyrrolo[3,2,1-*ij*]quinoline-10(7a*H*)-carboxylate (0.041 g, 18%) was prepared by the general method of Example 89, step C from *tert*-butyl (7a*S*,11a*R*)-2-bromo-5,6,7a,8,9,10,11,11a-octahydro-4*H*-

15 pyrido[3',4':4,5]pyrrolo[3,2,1-*ij*]quinoline-10(7a*H*)-carboxylate (0.20 g, 0.50 mmol), 2-(trifluoromethyl)phenyl boronic acid (0.19 g, 1.0 mmol), Pd(PPh₃)₂Cl₂ (17 mg, 0.025 mmol), Na₂CO₃ (2.0 M, 1.0 mL, 2.0 mmol) as a white foam. MS (ESI): 459 (base, M+H).

20 Step B:

The title compound (0.030 g, 94%) was prepared by the general method of Example 312, step B from *tert*-butyl (7a*S*,11a*R*)-2-[2-(trifluoromethyl)phenyl]-5,6,7a,8,9,10,11,11a-octahydro-4*H*-pyrido[3',4':4,5]pyrrolo[3,2,1-*ij*]quinoline-10(7a*H*)-carboxylate (0.041 g, 0.090 mmol) as a white foam. ¹H NMR (CDCl₃, 300
25 MHz) δ 1.80-2.08 (m, 2H), 2.08-2.28 (m, 2H), 2.43 (br, 1H), 2.60-2.80 (m, 4H), 2.85-2.98 (m, 2H), 3.07-3.20 (m, 2H), 3.25-3.40 (m, 1H), 3.40-3.48 (m, 1H), 6.84 (s, 1H), 6.88 (s, 1H), 7.34 (d, J=7.7 Hz, 1H), 7.40 (t, J=7.6 Hz, 1H), 7.51 (t, J=7.4 Hz, 1H), 7.71 (d, J=8.1 Hz, 1H) ppm. MS (ESI): 359 (base, M+H).

EXAMPLE 367

(7a*S*,11a*R*)-2-[4-isopropoxy-2-(trifluoromethyl)phenyl]-5,6,7a,8,9,10,11,11a-octahydro-4*H*-pyrido[3',4':4,5]pyrrolo[3,2,1-*ij*]quinoline

5 **Step A:**

Tert-butyl (7a*S*,11a*R*)-2-[4-isopropoxy-2-(trifluoromethyl)phenyl]-5,6,7a,8,9,10,11,11a-octahydro-4*H*-pyrido[3',4':4,5]pyrrolo[3,2,1-*ij*]quinoline-10(7a*H*)-carboxylate (0.16 g, 61%) was prepared by the general method of Example 89, step C from *tert-butyl* (7a*S*,11a*R*)-2-bromo-5,6,7a,8,9,10,11,11a-octahydro-4*H*-pyrido[3',4':4,5]pyrrolo[3,2,1-*ij*]quinoline-10(7a*H*)-carboxylate (0.20 g, 0.50 mmol), 4-isopropoxy-2-(trifluoromethyl)phenylboronic acid (0.18 g, 0.73 mmol), Pd(PPh₃)₂Cl₂ (17 mg, 0.025 mmol), Na₂CO₃ (2.0 M, 1.0 mL, 2.0 mmol) as a white foam. MS (ESI): 517 (base, M+H).

15 **Step B:**

The title compound (0.13 g, 100%) was prepared by the general method of Example 312, step B from *tert-butyl* (7a*S*,11a*R*)-2-[4-isopropoxy-2-(trifluoromethyl)phenyl]-5,6,7a,8,9,10,11,11a-octahydro-4*H*-pyrido[3',4':4,5]pyrrolo[3,2,1-*ij*]quinoline-10(7a*H*)-carboxylate (0.16 g, 0.31 mmol) as a white foam. ¹H NMR (CDCl₃, 300 MHz) δ 1.38 (d, J=6.0 Hz, 6H), 1.70-1.88 (m, 1H), 1.88-2.00 (m, 1H), 2.02-2.18 (m, 3H), 2.55-2.80 (m, 4H), 2.80-2.98 (m, 2H), 3.00-3.13 (m, 2H), 3.25-3.37 (m, 1H), 3.38-3.55 (m, 1H), 4.61, (p, J=6.0 Hz, 1H), 6.81 (s, 1H), 6.85 (s, 1H), 7.01 (dd, J=1.2, 8.6 Hz, 1H), 7.18-7.26 (m, 2H) ppm. MS (ESI): 417 (base, M+H).

25

EXAMPLE 368

(7a*S*,11a*R*)-2-[2,4-bis(trifluoromethyl)phenyl]-5,6,7a,8,9,10,11,11a-octahydro-4*H*-pyrido[3',4':4,5]pyrrolo[3,2,1-*ij*]quinoline

5 **Step A:**

Tert-butyl (7a*S*,11a*R*)-2-[2,4-bis(trifluoromethyl)phenyl]-5,6,7a,8,9,10,11,11a-octahydro-4*H*-pyrido[3',4':4,5]pyrrolo[3,2,1-*ij*]quinoline-10(7a*H*)-carboxylate (0.029 g, 11%) was prepared by the general method of Example 89, step C from *tert*-butyl (7a*S*,11a*R*)-2-bromo-5,6,7a,8,9,10,11,11a-octahydro-4*H*-pyrido[3',4':4,5]pyrrolo[3,2,1-*ij*]quinoline-10(7a*H*)-carboxylate (0.20 g, 0.50 mmol), 2,4-bis(trifluoromethyl)phenylboronic acid (0.26 g, 1.0 mmol), Pd(PPh₃)₂Cl₂ (17 mg, 0.025 mmol), Na₂CO₃ (2.0 M, 1.0 mL, 2.0 mmol) as a white foam. MS (ESI): 527 (base, M+H).

15 **Step B:**

The title compound (0.023 g, 100%) was prepared by the general method of Example 312, step B from *tert*-butyl (7a*S*,11a*R*)-2-[2,4-bis(trifluoromethyl)phenyl]-5,6,7a,8,9,10,11,11a-octahydro-4*H*-pyrido[3',4':4,5]pyrrolo[3,2,1-*ij*]quinoline-10(7a*H*)-carboxylate (0.029 g, 0.055 mmol) as a white foam. ¹H NMR (CDCl₃, 300 MHz) δ 2.10-2.30 (m, 4H), 2.50-2.70 (m, 3H), 2.70-2.86 (m, 3H), 3.10-3.55 (m, 5H), 6.90 (s, 2H), 7.45 (d, J=7.8 Hz, 1H), 7.78 (d, J=7.8 Hz, 1H), 7.97 (s, 1H) ppm. MS (ESI): 427 (base, M+H).

EXAMPLE 369

25 (7a*S*,11a*R*)-2-[4-fluoro-2-(trifluoromethyl)phenyl]-5,6,7a,8,9,10,11,11a-octahydro-4*H*-pyrido[3',4':4,5]pyrrolo[3,2,1-*ij*]quinoline

Step A:

30 *Tert-butyl* (7a*S*,11a*R*)-2-[4-fluoro-2-(trifluoromethyl)phenyl]-5,6,7a,8,9,10,11,11a-octahydro-4*H*-pyrido[3',4':4,5]pyrrolo[3,2,1-*ij*]quinoline-10(7a*H*)-carboxylate (0.093 g, 75%) was prepared by the general method of Example

319, step A from *tert*-butyl (7a*S*,11a*R*)-2-bromo-5,6,7a,8,9,10,11,11a-octahydro-4*H*-pyrido[3',4':4,5]pyrrolo[3,2,1-*ij*]quinoline-10(7a*H*)-carboxylate (0.10 g, 0.26 mmol), 4-fluoro-2-(trifluoromethyl)phenylboronic acid (0.11 g, 0.51 mmol), Pd(PPh₃)₄ (12 mg, 0.010 mmol), and Ba(OH)₂ (0.17 M, 3.0 mL, 0.51 mmol) as a white foam. MS (ESI): 477 (base, M+H).

Step B:

The title compound (0.071 g, 97%) was prepared by the general method of Example 312, step B from *tert*-butyl (7a*S*,11a*R*)-2-[4-fluoro-2-(trifluoromethyl)phenyl]-5,6,7a,8,9,10,11,11a-octahydro-4*H*-pyrido[3',4':4,5]pyrrolo[3,2,1-*ij*]quinoline-10(7a*H*)-carboxylate (0.093 g, 0.19 mmol) as a white foam. ¹H NMR (CDCl₃, 300 MHz) δ 2.08-2.12 (m, 4H), 2.58-2.85 (m, 4H), 3.02-3.24 (m, 2H), 3.28-3.50 (m, 5H), 7.11 (s, 1H), 7.12 (s, 1H), 7.21 (t, J=9.4 Hz, 1H), 7.58-7.68 (m, 1H), 7.68-7.75 (m, 1H) ppm. MS (ESI): 377 (base, M+H).

EXAMPLE 370

4-[(7a*S*,11a*R*)-5,6,7a,8,9,10,11,11a-octahydro-4*H*-pyrido[3',4':4,5]pyrrolo[3,2,1-*ij*]quinolin-2-yl]-3-(trifluoromethyl)aniline

Step A:

Tert-butyl (7a*S*,11a*R*)-2-[4-[(*tert*-butoxycarbonyl)amino]-2-(trifluoromethyl)phenyl]-5,6,7a,8,9,10,11,11a-octahydro-4*H*-pyrido[3',4':4,5]pyrrolo[3,2,1-*ij*]quinoline-10(7a*H*)-carboxylate (0.13 g, 93%) was prepared by the general method of Example 319, step A from *tert*-butyl (7a*S*,11a*R*)-2-bromo-5,6,7a,8,9,10,11,11a-octahydro-4*H*-pyrido[3',4':4,5]pyrrolo[3,2,1-*ij*]quinoline-10(7a*H*)-carboxylate (0.10 g, 0.25 mmol), 4-[(*tert*-butoxycarbonyl)amino]-2-(trifluoromethyl)phenylboronic acid (0.15 g, 0.50 mmol), Pd(PPh₃)₄ (12 mg, 0.010 mmol), and Ba(OH)₂ (0.17 M, 3.0 mL, 0.51 mmol) as a white foam. MS (ESI): 574 (base, M+H).

Step B:

The title compound (0.079 g, 72%) was prepared by the general method of Example 312, step B from *tert*-butyl (7a*S*,11a*R*)-2-[4-[(*tert*-butoxycarbonyl)amino]-2-(trifluoromethyl)phenyl]-5,6,7a,8,9,10,11,11a-octahydro-4*H*-

5 pyrido[3',4':4,5]pyrrolo[3,2,1-*ij*]quinoline-10(7a*H*)-carboxylate (0.13 g, 0.23 mmol) as a white foam. ¹H NMR (CDCl₃, 300 MHz) δ 1.78-2.00 (m, 2H), 2.05-2.22 (m, 2H), 2.58-2.80 (m, 4H), 2.80-2.98 (m, 2H), 3.04-3.16 (m, 2H), 3.28-3.38 (m, 1H), 3.38-3.48 (m, 1H), 3.82 (br, 3H), 6.72-6.88 (m, 3H), 7.00 (d, J=2.6 Hz, 1H), 7.11 (d, J=8.1 Hz, 1H) ppm. MS (ESI): 374 (base, M+H).

10

EXAMPLE 371

4-[(7a*S*,11a*R*)-5,6,7a,8,9,10,11,11a-octahydro-4*H*-pyrido[3',4':4,5]pyrrolo[3,2,1-*ij*]quinolin-2-yl]-*N*-methyl-3-(trifluoromethyl)aniline

15 **Step A:**

Tert-butyl (7a*S*,11a*R*)-2-[4-[(*tert*-butoxycarbonyl)(methyl)amino]-2-(trifluoromethyl)phenyl]-5,6,7a,8,9,10,11,11a-octahydro-4*H*-pyrido[3',4':4,5]pyrrolo[3,2,1-*ij*]quinoline-10(7a*H*)-carboxylate (0.12 g, 82%) was prepared by the general method of Example 319, step A from *tert*-butyl (7a*S*,11a*R*)-2-bromo-5,6,7a,8,9,10,11,11a-octahydro-4*H*-pyrido[3',4':4,5]pyrrolo[3,2,1-*ij*]quinoline-10(7a*H*)-carboxylate (0.10 g, 0.25 mmol), 4-[(*tert*-butoxycarbonyl)(methyl)amino]-2-(trifluoromethyl)phenylboronic acid (0.16 g, 0.50 mmol), Pd(PPh₃)₄ (12 mg, 0.010 mmol), and Ba(OH)₂ (0.17 M, 3.0 mL, 0.51 mmol) as a white foam. MS (ESI): 588 (base, M+H).

25

Step B:

The title compound (0.071g, 71%) was prepared by the general method of Example 312, step B from *tert*-butyl (7a*S*,11a*R*)-2-[4-[(*tert*-butoxycarbonyl)(methyl)amino]-2-(trifluoromethyl)phenyl]-5,6,7a,8,9,10,11,11a-octahydro-4*H*-pyrido[3',4':4,5]pyrrolo[3,2,1-*ij*]quinoline-10(7a*H*)-carboxylate (0.12 g, 0.20 mmol) as a white foam. ¹H NMR (CDCl₃, 300 MHz) δ 1.78-2.00 (m, 2H),

30

2.05-2.25 (m, 2H), 2.60-2.80 (m, 4H), 2.80-3.00 (m, 5H), 3.00-3.20 (m, 2H), 3.28-3.40 (m, 1H), 3.40-3.50 (m, 1H), 3.91 (br, 2H), 6.73 (dd, J=2.6, 8.3 Hz, 1H), 6.81 (s, 1H), 6.85 (s, 1H), 6.91 (d, J=2.6 Hz, 1H), 7.15 (d, J=8.3 Hz, 1H) ppm. MS (ESI): 388 (base, M+H).

5

EXAMPLE 372

4-[(7a*S*,11a*R*)-5,6,7a,8,9,10,11,11a-octahydro-4*H*-pyrido[3',4':4,5]pyrrolo[3,2,1-*ij*]quinolin-2-yl]-3-methylbenzonitrile

10 Step A:

Tert-butyl (7a*S*,11a*R*)-2-(4-cyano-2-methylphenyl)-5,6,7a,8,9,10,11,11a-octahydro-4*H*-pyrido[3',4':4,5]pyrrolo[3,2,1-*ij*]quinoline-10(7a*H*)-carboxylate (0.073 g, 65%) was prepared by the general method of Example 319, step A from *tert*-butyl (7a*S*,11a*R*)-2-bromo-5,6,7a,8,9,10,11,11a-octahydro-4*H*-

15 pyrido[3',4':4,5]pyrrolo[3,2,1-*ij*]quinoline-10(7a*H*)-carboxylate (0.10 g, 0.26 mmol), 4-cyano-2-methylphenylboronic acid (0.088 g, 0.52 mmol), Pd(PPh₃)₄ (12 mg, 0.010 mmol), and Ba(OH)₂ (0.17 M, 3.0 mL, 0.51 mmol) as a white foam. MS (ESI): 430 (base, M+H).

20 Step B:

The title compound (0.050 g, 89%) was prepared by the general method of Example 312, step B from *tert*-butyl (7a*S*,11a*R*)-2-(4-cyano-2-methylphenyl)-5,6,7a,8,9,10,11,11a-octahydro-4*H*-pyrido[3',4':4,5]pyrrolo[3,2,1-*ij*]quinoline-10(7a*H*)-carboxylate (0.073 g, 0.17 mmol) as a white foam. ¹H NMR (CDCl₃, 300

25 MHz) δ 2.10-2.20 (m, 4H), 2.30 (s, 3H), 2.55-2.70 (m, 1H), 2.70-2.80 (m, 3H), 3.07-3.26 (m, 2H), 3.26-3.48 (m, 5H), 6.84 (s, 2H), 7.25 (d, J=7.7 Hz, 1H), 7.47 (d, J=7.7 Hz, 1H), 7.51 (s, 1H) ppm. MS (ESI): 330 (base, M+H).

EXAMPLE 373

2-[(7a*S*,11a*R*)-5,6,7a,8,9,10,11,11a-octahydro-4*H*-pyrido[3',4':4,5]pyrrolo[3,2,1-*ij*]quinolin-2-yl]benzaldehyde

5 **Step A:**

Tert-butyl (7a*S*,11a*R*)-2-(2-formylphenyl)-5,6,7a,8,9,10,11,11a-octahydro-4*H*-pyrido[3',4':4,5]pyrrolo[3,2,1-*ij*]quinoline-10(7a*H*)-carboxylate (0.091 g, 44%) was prepared by the general method of Example 89, step C from *tert-butyl* (7a*S*,11a*R*)-2-bromo-5,6,7a,8,9,10,11,11a-octahydro-4*H*-pyrido[3',4':4,5]pyrrolo[3,2,1-*ij*]quinoline-10(7a*H*)-carboxylate (0.20 g, 0.50 mmol), 2-formylphenylboronic acid (0.15 g, 1.0 mmol), Pd(PPh₃)₂Cl₂ (17 mg, 0.025 mmol), Na₂CO₃ (2.0 M, 1.0 mL, 2.0 mmol) as a white foam. MS (ESI): 419 (base, M+H).

Step B:

15 The title compound (0.021 g, 91%) was prepared by the general method of Example 312, step B from *tert-butyl* (7a*S*,11a*R*)-2-(2-formylphenyl)-5,6,7a,8,9,10,11,11a-octahydro-4*H*-pyrido[3',4':4,5]pyrrolo[3,2,1-*ij*]quinoline-10(7a*H*)-carboxylate (0.030 g, 0.070 mmol) as a white foam. ¹H NMR (CDCl₃, 300 MHz) δ 1.94-2.24 (m, 4H), 2.59-2.82 (m, 5H), 3.00-3.24 (m, 2H), 3.28-3.42 (m, 3H), 3.44-3.52 (m, 1H), 6.90 (s, 1H), 6.97 (s, 1H), 7.38-7.46 (m, 2H), 7.66 (td, J=7.5, 1.4 Hz, 1H), 7.99 (dd, J=1.4, 8.0 Hz, 1H), 10.01 (s, 1H) ppm. MS (ESI): 319 (base, M+H).

EXAMPLE 374

25 **{2-[(7a*S*,11a*R*)-5,6,7a,8,9,10,11,11a-octahydro-4*H*-pyrido[3',4':4,5]pyrrolo[3,2,1-*ij*]quinolin-2-yl]phenyl}methanol**

Step A:

30 *Tert-butyl* (7a*S*,11a*R*)-2-[2-(hydroxymethyl)phenyl]-5,6,7a,8,9,10,11,11a-octahydro-4*H*-pyrido[3',4':4,5]pyrrolo[3,2,1-*ij*]quinoline-10(7a*H*)-carboxylate (0.42 g, 69%) was prepared by the method of Example 341 from *tert-butyl* (7a*S*,11a*R*)-2-(2-

formylphenyl)-5,6,7a,8,9,10,11,11a-octahydro-4*H*-pyrido[3',4':4,5]pyrrolo[3,2,1-*ij*]quinoline-10(7*aH*)-carboxylate (0.061 g, 0.15 mmol) and NaBH₄ (0.060 g, 1.6 mmol) as a white solid. MS (ESI): 421 (base, M+H).

5 Step B:

The title compound (0.032 g, 100%) was prepared by the general method of Example 312, step B from *tert*-butyl (7*aS*,11*aR*)-2-[2-(hydroxymethyl)phenyl]-5,6,7a,8,9,10,11,11a-octahydro-4*H*-pyrido[3',4':4,5]pyrrolo[3,2,1-*ij*]quinoline-10(7*aH*)-carboxylate (0.042 g, 0.10 mmol) as a white foam. ¹H NMR (CDCl₃, 300
10 MHz) δ 1.80-2.04 (m, 2H), 2.08-2.20 (m, 2H), 2.50-2.80 (m, 4H), 2.82-2.97 (m, 2H), 3.04-3.20 (m, 2H), 3.20-3.38 (m, 1H), 3.38-3.42 (m, 1H), 4.65 (s, 2H), 6.89 (s, 1H), 6.93 (s, 1H), 7.22-7.38 (m, 3H), 7.50-7.57 (m, 1H) ppm. MS (ESI): 321 (base, M+H).

EXAMPLE 375

15 2-[(7*aS*,11*aR*)-5,6,7a,8,9,10,11,11a-octahydro-4*H*-pyrido[3',4':4,5]pyrrolo[3,2,1-*ij*]quinolin-2-yl]-5-methoxybenzaldehyde

Step A:

Tert-butyl (7*aS*,11*aR*)-2-(2-formyl-4-methoxyphenyl)-5,6,7a,8,9,10,11,11a-octahydro-4*H*-pyrido[3',4':4,5]pyrrolo[3,2,1-*ij*]quinoline-10(7*aH*)-carboxylate (0.084
20 g, 38%) was prepared by the general method of Example 89, step C from *tert*-butyl (7*aS*,11*aR*)-2-bromo-5,6,7a,8,9,10,11,11a-octahydro-4*H*-pyrido[3',4':4,5]pyrrolo[3,2,1-*ij*]quinoline-10(7*aH*)-carboxylate (0.20 g, 0.50 mmol), 2-formyl-4-methoxyphenylboronic acid (0.18 g, 1.0 mmol), Pd(PPh₃)₂Cl₂ (17 mg,
25 0.025 mmol), Na₂CO₃ (2.0 M, 1.0 mL, 2.0 mmol) as a white foam. MS (ESI): 449 (base, M+H).

Step B:

The title compound (0.056 g, 86%) was prepared by the general method of
30 Example 312, step B from *tert*-butyl (7*aS*,11*aR*)-2-(2-formyl-4-methoxyphenyl)-5,6,7a,8,9,10,11,11a-octahydro-4*H*-pyrido[3',4':4,5]pyrrolo[3,2,1-*ij*]quinoline-

10(7a*H*)-carboxylate (0.084 g, 0.19 mmol) as a white foam. ¹H NMR (CDCl₃, 300 MHz) δ 2.00-2.10 (m, 2H), 2.10-2.25 (m, 2H), 2.59-2.82 (m, 4H), 2.98-3.20 (m, 2H), 3.20-3.40 (m, 3H), 3.42-3.52 (m, 2H), 3.92 (s, 3H), 6.86 (s, 1H), 6.92 (s, 1H), 7.18 (dd, J=8.4, 2.6 Hz, 1H), 7.35 (d, J=8.4 Hz, 1H), 7.47 (d, J=2.6 Hz, 1H), 9.97 (s, 1H) ppm. MS (ESI): 349 (base, M+H).

EXAMPLE 376

{2-[(7a*S*,11a*R*)-5,6,7a,8,9,10,11,11a-octahydro-4*H*-pyrido[3',4':4,5]pyrrolo[3,2,1-*ij*]quinolin-2-yl]-5-methoxyphenyl}methanol

10

Step A:

Tert-butyl (7a*S*,11a*R*)-2-[2-(hydroxymethyl)-4-methoxyphenyl]-5,6,7a,8,9,10,11,11a-octahydro-4*H*-pyrido[3',4':4,5]pyrrolo[3,2,1-*ij*]quinoline-10(7a*H*)-carboxylate (0.016 g) was obtained as a byproduct of Example 375. MS (ESI): 451 (base, M+H).

15

Step B:

The title compound (0.010 g, 83%) was prepared by the general method of Example 312, step B from *tert-butyl* (7a*S*,11a*R*)-2-[2-(hydroxymethyl)-4-methoxyphenyl]-5,6,7a,8,9,10,11,11a-octahydro-4*H*-pyrido[3',4':4,5]pyrrolo[3,2,1-*ij*]quinoline-10(7a*H*)-carboxylate (0.016 g, 0.036 mmol) as a white foam. ¹H NMR (CDCl₃, 300 MHz) δ 1.70-2.02 (m, 2H), 2.08-2.20 (m, 2H), 2.50-2.80 (m, 4H), 2.80-2.95 (m, 2H), 3.00-3.14 (m, 2H), 3.28-3.38 (m, 1H), 3.38-3.46 (m, 1H), 3.87 (s, 3H), 4.65 (s, 2H), 6.80-6.90 (m, 3H), 7.10 (d, J=3.0 Hz, 1H), 7.19 (d, J=8.4 Hz, 1H) ppm. MS (ESI): 351 (base, M+H).

25

EXAMPLE 377

(8a*S*,12a*R*)-2-[4-ethoxy-2-(trifluoromethyl)phenyl]-4,5,6,7,8a,9,10,11,12,12a-decahydroazepino[3,2,1-*hi*]pyrido[4,3*b*]indole

5 The title compound was afforded as a yellow oil (81 mg, 79%) according to the method of Example 319, step A followed by Example 312, step B from *tert*-butyl (8a*S*,12a*R*)-2-bromo-4,5,6,7,9,10,12,12a-octahydroazepino[3,2,1-*hi*]pyrido[4,3*b*]indole-11(8*H*)-carboxylate (100 mg, 0.25 mmol) and 4-ethoxy-2-(trifluoromethyl)phenylboronic acid (83 mg, 0.5 mmol). ¹H NMR (CDCl₃) δ 1.37 (t, 3H, *J* = 7.0 Hz), 1.44-1.58 (m, 1H), 1.66-1.84 (m, 2H), 1.89-2.00 (m, 3H), 2.42-2.73 (m, 3H), 2.80-3.04 (m, 5H), 3.10-3.36 (m, 3H), 4.01 (q, 2H, *J* = 7.00 Hz), 6.77 (d, 2H, *J* = 5.2 Hz), 6.94 (dd, 1H, *J* = 2.5, 8.5 Hz), 7.13-7.19 (m, 2H) ppm. MS (ESI): 417 (base, M + H).

15

EXAMPLE 378

(7a*S*,11a*R*)-2-[4-ethoxy-2-(trifluoromethyl)phenyl]-5,6,7a,8,9,10,11,11a-octahydro-4*H*-pyrido[3',4':4,5]pyrrolo[3,2,1-*ij*]quinoline

20 The title compound was afforded as a yellow oil (56 mg, 56%) according to the method of Example 319, step A followed by Example 312, step B from *tert*-butyl (7a*S*,11a*R*)-2-bromo-5,6,8,9,11,11a-hexahydro-4*H*-pyrido[3',4':4,5]pyrrolo[3,2,1-*ij*]quinoline-10(7a*H*)-carboxylate (100 mg, 0.25 mmol) and 4-methoxy-2-(trifluoromethyl)phenylboronic acid (76 mg, 0.5 mmol). ¹H NMR (CDCl₃) δ 1.46 (t, 3H, *J* = 7.0 Hz), 1.86-2.03 (m, 2H), 2.10-2.21 (m, 2H), 2.62-2.80 (m, 5H), 2.84-2.96 (m, 2H), 3.09-3.19 (m, 2H), 3.33-3.39 (m, 1H), 3.42-3.47 (m, 1H), 4.10 (q, 2H, *J* = 7.0 Hz), 6.83 (d, 2H, *J* = 11.0 Hz), 7.02 (dd, 1H, *J* = 2.7, 8.3 Hz), 7.16-7.28 (m, 2H) ppm. MS (ESI): 403 (base, M + H).

EXAMPLE 379

(8a*S*,12a*R*)-2-[3-chloro-2-methylphenyl]-4,5,6,7,8a,9,10,11,12,12a-decahydroazepino[3,2,1-*hi*]pyrido[4,3*b*]indole

5 The title compound was afforded as a yellow oil (49 mg, 53%) according to the method of Example 319, step A followed by Example 312, step B from *tert*-butyl (8a*S*,12a*R*)-2-bromo-4,5,6,7,9,10,12,12a-octahydroazepino[3,2,1-*hi*]pyrido[4,3*b*]indole-11(8*H*)-carboxylate (100 mg, 0.24 mmol) and 3-chloro-2-methylphenylboronic acid (84 mg, 0.48 mmol). MS (ESI): 353 (base, M + H).

10

EXAMPLE 380

(7a*S*,11a*R*)-2-[3-chloro-2-methylphenyl]-5,6,7a,8,9,10,11,11a-octahydro-4*H*-pyrido[3',4':4,5]pyrrolo[3,2,1-*ij*]quinoline

15 The title compound was afforded as a yellow oil (55 mg, 65%) according to the method of Example 319, step A followed by Example 312, step B from *tert*-butyl (7a*S*,11a*R*)-2-bromo-5,6,8,9,11,11a-hexahydro-4*H*-pyrido[3',4':4,5]pyrrolo[3,2,1-*ij*]quinoline-10(7a*H*)-carboxylate (100 mg, 0.24 mmol) and 3-chloro-2-methylphenylboronic acid (80 mg, 0.48 mmol). MS (ESI): 339 (base, M + H).

20

EXAMPLE 381

(7a*S*,11a*R*)-2-[5-fluoro-2-methylphenyl]-5,6,7a,8,9,10,11,11a-octahydro-4*H*-pyrido[3',4':4,5]pyrrolo[3,2,1-*ij*]quinoline

25 The title compound was afforded as a yellow oil (29 mg, 91%) according to the method of Example 319, step A followed by Example 312, step B from *tert*-butyl (7a*S*,11a*R*)-2-bromo-5,6,8,9,11,11a-hexahydro-4*H*-pyrido[3',4':4,5]pyrrolo[3,2,1-*ij*]quinoline-10(7a*H*)-carboxylate (50 mg, 0.13 mmol) and 5-fluoro-2-methylphenylboronic acid (39 mg, 0.25 mmol). MS (ESI): 323 (base, M + H).

30

EXAMPLE 382

(±)-cis-2-(2,3-dichlorophenyl)-10-propyl-5,6,7a,8,9,10,11,11a-octahydro-4H-pyrido[3',4':4,5]pyrrolo[3,2,1-ij]quinoline

5 To a solution of (±)-cis-2-(2,3-dichlorophenyl)-5,6,7a,8,9,10,11,11a-octahydro-4H-pyrido[3',4':4,5]pyrrolo[3,2,1-ij]quinoline (30 mg, 0.083 mmol) in 1,4-dioxane (0.5 mL) and *N,N*-diisopropylethylamine (108 mg, 0.83 mmol) were added 1-bromopropane (21 mg, 0.17 mmol) and KI (catalytic amount). The reaction mixture was heated at 100 °C for 15h. The reaction mixture was cooled to 20°C then
10 concentrated *in vacuo* and chromatographed on a silica gel column by elution with CHCl₃/MeOH (99/1) to give the title compound (27 mg, 82%) as a yellow oil. ¹H NMR (CDCl₃, 300 MHz) δ 0.92(t, J = 7.3 Hz, 3H), 1.58-1.75 (br, 2H), 2.03-2.23 (m, 5H), 2.42-2.55 (br, 2H), 2.58-2.67 (m, 1H), 2.75 (t, J = 7.4 Hz, 2H), 2.85-2.95 (br, 1H), 2.98-3.12 (br, 1H), 3.31 (dt, J = 10.3, 3.6 Hz, 1H), 3.37-3.45 (br, 2H), 6.94 (s,
15 1H), 6.97 (s, 1H), 7.15-7.20 (m, 2H), 7.36-7.42 (m, 1H) ppm.

EXAMPLE 383

(7a*S*,11a*R*)-2-(2,3-dichlorophenyl)-10-propyl-5,6,7a,8,9,10,11,11a-octahydro-4H-pyrido[3',4':4,5]pyrrolo[3,2,1-ij]quinoline

20

The title compound was prepared by the method of Example 382 as a yellow oil (22 mg, 66%) from (7a*S*,11a*R*)-2-(2,3-dichlorophenyl)-5,6,7a,8,9,10,11,11a-octahydro-4H-pyrido[3',4':4,5]pyrrolo[3,2,1-ij]quinoline (30 mg, 0.083 mmol). The title compound was spectroscopically identical to Example 382. MS (CI, NH₃): 401.1
25 (base, M+H).

EXAMPLE 384**(±)-*cis*-10-butyl-2-(2,3-dichlorophenyl)-5,6,7a,8,9,10,11,11a-octahydro-4*H*-pyrido[3',4':4,5]pyrrolo[3,2,1-*ij*]quinoline**

5 The title compound was prepared by the method of Example 382 as a yellow oil (28 mg, 82%) from (±)-*cis*-2-(2,3-dichlorophenyl)-5,6,7a,8,9,10,11,11a-octahydro-4*H*-pyrido[3',4':4,5]pyrrolo[3,2,1-*ij*]quinoline (30 mg, 0.083 mmol) and 1-bromobutane (23 mg, 0.17 mmol). ¹H NMR (CDCl₃, 300 MHz) δ 0.92(t, J = 7.3 Hz, 3H), 1.32 (se, J = 7.3 Hz, 2H), 1.53-1.65 (br, 2H), 2.02-2.25 (m, 5H), 2.38-2.53 (br, 2H), 2.58-2.68 (m, 1H), 2.75 (t, J = 6.4 Hz, 2H), 2.80-2.92 (br, 1H), 2.95-3.07 (br, 10 1H), 3.31 (dt, J = 10.3, 3.6 Hz, 1H), 3.37-3.45 (br, 2H), 6.94 (s, 1H), 6.99 (s, 1H), 7.15-7.21 (m, 2H), 7.35-7.40 (m, 1H) ppm.

EXAMPLE 385**15 (7a*S*,11a*R*)-10-butyl-2-(2,3-dichlorophenyl)-5,6,7a,8,9,10,11,11a-octahydro-4*H*-pyrido[3',4':4,5]pyrrolo[3,2,1-*ij*]quinoline**

 The title compound was prepared by the method of Example 382 as a yellow oil (23 mg, 62%) from (7a*S*,11a*R*)-2-(2,3-dichlorophenyl)-5,6,7a,8,9,10,11,11a-octahydro-4*H*-pyrido[3',4':4,5]pyrrolo[3,2,1-*ij*]quinoline (30 mg, 0.083 mmol). The 20 title compound was spectroscopically identical to Example 384. MS (CI, NH₃): 415.1 (base, M+H).

EXAMPLE 386**25 (7a*S*,11a*R*)-2-(2,3-dichlorophenyl)-10-(4-pentenyl)-5,6,7a,8,9,10,11,11a-octahydro-4*H*-pyrido[3',4':4,5]pyrrolo[3,2,1-*ij*]quinoline**

 The title compound was prepared by the method of Example 382 as a yellow oil (22 mg, 62%) from (7a*S*,11a*R*)-2-(2,3-dichlorophenyl)-5,6,7a,8,9,10,11,11a-octahydro-4*H*-pyrido[3',4':4,5]pyrrolo[3,2,1-*ij*]quinoline (30 mg, 0.083 mmol) and 5-bromo-1-pentene (25 mg, 0.17 mmol). ¹H NMR (CDCl₃, 300 MHz) δ 1.62-1.75 (br, 30

2H), 2.01-2.22 (m, 7H), 2.35-2.53 (br, 3H), 2.58-2.65 (m, 1H), 2.74 (t, J = 6.6 Hz, 2H), 2.75-2.85 (br, 1H), 2.88-3.05 (br, 1H), 3.28-3.41 (m, 3H), 4.97 (d, J = 13.5 Hz, 1H), 5.02 (dd, J = 17.6, 1.5 Hz, 1H), 5.73-5.83 (m, 1H), 6.93 (s, 1H), 6.98 (s, 1H), 7.15-7.21 (m, 2H), 7.36-7.40 (m, 1H) ppm. MS (CI, NH₃): 427.1 (base, M+H).

5

EXAMPLE 387

(7a*S*,11a*R*)-2-(2,3-dichlorophenyl)-10-(3-methyl-2-butenyl)-5,6,7a,8,9,10,11,11a-octahydro-4*H*-pyrido[3',4':4,5]pyrrolo[3,2,1-*ij*]quinoline

10 The title compound was prepared by the method of Example 382 as a yellow oil (27 mg, 76%) from (7a*S*,11a*R*)-2-(2,3-dichlorophenyl)-5,6,7a,8,9,10,11,11a-octahydro-4*H*-pyrido[3',4':4,5]pyrrolo[3,2,1-*ij*]quinoline (30 mg, 0.083 mmol) and 4-bromo-2-methyl-2-butene (25 mg, 0.17 mmol). MS (CI, NH₃): 427.1 (base, M+H).

15

EXAMPLE 388

(7a*S*,11a*R*)-2-(2,4-dichlorophenyl)-10-propyl-5,6,7a,8,9,10,11,11a-octahydro-4*H*-pyrido[3',4':4,5]pyrrolo[3,2,1-*ij*]quinoline

20 The title compound was prepared by the method of Example 382 as a yellow oil (21 mg, 65%) from (7a*S*,11a*R*)-2-(2,4-dichlorophenyl)-5,6,7a,8,9,10,11,11a-octahydro-4*H*-pyrido[3',4':4,5]pyrrolo[3,2,1-*ij*]quinoline (30 mg, 0.083 mmol) and 1-bromopropane (30 mg, 0.24 mmol). ¹H NMR (CDCl₃, 300 MHz) δ 0.92 (t, J = 7.3 Hz, 3H), 1.61-1.75 (m, 2H), 2.02-2.35 (m, 6H), 2.45-2.63 (m, 3H), 2.75 (t, J = 6.5 Hz, 2H), 2.87-2.98 (br, 1H), 3.00-3.08 (br, 1H), 3.30 (dt, J = 10.6, 4.0 Hz, 1H), 3.35-3.48 (m, 2H), 6.94 (s, 1H), 6.99 (s, 1H), 7.21-7.25 (m, 1H), 7.44 (d, J = 1.5 Hz, 1H) ppm. MS (CI, NH₃): 401.1 (base, M+H).

25

EXAMPLE 389

(7a*S*,11a*R*)-10-butyl-2-(2,4-dichlorophenyl)-5,6,7a,8,9,10,11,11a-octahydro-4*H*-pyrido[3',4':4,5]pyrrolo[3,2,1-*ij*]quinoline

5 The title compound was prepared by the method of Example 382 as a yellow oil (21 mg, 61%) from (7a*S*,11a*R*)-2-(2,4-dichlorophenyl)-5,6,7a,8,9,10,11,11a-octahydro-4*H*-pyrido[3',4':4,5]pyrrolo[3,2,1-*ij*]quinoline (30 mg, 0.083 mmol) and 1-bromobutane (23 mg, 0.17 mmol). MS (CI, NH₃): 415.1 (base, M+H).

10

EXAMPLE 390

(7a*S*,11a*R*)-2-(2,4-dichlorophenyl)-10-(4-pentenyl)-5,6,7a,8,9,10,11,11a-octahydro-4*H*-pyrido[3',4':4,5]pyrrolo[3,2,1-*ij*]quinoline

15 The title compound was prepared by the method of Example 382 as a yellow oil (23 mg, 67%) from (7a*S*,11a*R*)-2-(2,4-dichlorophenyl)-5,6,7a,8,9,10,11,11a-octahydro-4*H*-pyrido[3',4':4,5]pyrrolo[3,2,1-*ij*]quinoline (30 mg, 0.083 mmol) and 5-bromo-1-pentene (25 mg, 0.16 mmol). MS (CI, NH₃): 427.1 (base, M+H).

EXAMPLE 391

20 **(7a*S*,11a*R*)-2-(2,4-dichlorophenyl)-10-(3-methyl-2-butenyl)-5,6,7a,8,9,10,11,11a-octahydro-4*H*-pyrido[3',4':4,5]pyrrolo[3,2,1-*ij*]quinoline**

25 The title compound was prepared by the method of Example 382 as a yellow oil (26 mg, 76%) from (7a*S*,11a*R*)-2-(2,4-dichlorophenyl)-5,6,7a,8,9,10,11,11a-octahydro-4*H*-pyrido[3',4':4,5]pyrrolo[3,2,1-*ij*]quinoline (30 mg, 0.083 mmol) and 4-bromo-2-methyl-2-butene (25 mg, 0.16 mmol). ¹H NMR (CDCl₃, 300 MHz) δ 1.68 (s, 3H), 1.81 (s, 3H), 2.12-2.23 (m, 3H), 2.26-2.42 (m, 1H), 2.55-2.70 (m, 2H), 2.78 (t, J = 6.6 Hz, 2H), 3.10-3.45 (m, 6H), 3.63-3.77 (m, 2H), 5.42-5.55 (br, 1H), 6.99 (s, 1H), 7.03 (s, 1H), 7.24-7.217.29 (m, 2H), 7.47 (d, J = 1.8 Hz, 1H) ppm. MS (CI, NH₃): 427.1 (base, M+H).

30

EXAMPLE 392

(7a*S*,11a*R*)-10-(cyclobutylmethyl)-2-(2,3-dichlorophenyl)-5,6,7a,8,9,10,11,11a-octahydro-4*H*-pyrido[3',4':4,5]pyrrolo[3,2,1-*ij*]quinoline

5 The title compound was prepared by the method of Example 382 as a yellow oil (22 mg, 58%) from (7a*S*,11a*R*)-2-(2,4-dichlorophenyl)-5,6,7a,8,9,10,11,11a-octahydro-4*H*-pyrido[3',4':4,5]pyrrolo[3,2,1-*ij*]quinoline (32 mg, 0.089 mmol) and (bromomethyl)cyclobutane (27 mg, 0.18 mmol). MS (CI, NH₃): 427.1 (base, M+H).

10

EXAMPLE 393

(7a*S*,11a*R*)-2-[4-methoxy-2-(trifluoromethyl)phenyl]-10-methyl-5,6,7a,8,9,10,11,11a-octahydro-4*H*-pyrido[3',4':4,5]pyrrolo[3,2,1-*ij*]quinoline

15 The solution of (7a*S*,11a*R*)-2-[4-methoxy-2-(trifluoromethyl)phenyl]-5,6,7a,8,9,10,11,11a-octahydro-4*H*-pyrido[3',4':4,5]pyrrolo[3,2,1-*ij*]quinoline (30 mg, 0.077 mmol) in formaldehyde (37 wt % aqueous solution, 97 mg, 1.16 mmol) and formic acid (54 mg, 1.16 mmol) was heated at 80 °C for 2h. The reaction mixture was diluted with H₂O then basified with 1N NaOH to pH 12 and extract with CHCl₃. The combined organic solution was dried over MgSO₄, concentrated *in vacuo*, and the
20 residue was chromatographed (silica gel; CHCl₃: MeOH 99:1-95:5) to give the title compound as a pale yellow oil (19 mg, 61%). MS (CI, NH₃): 403.1 (base, M+H).

EXAMPLE 394

25 **(7a*S*,11a*R*)-10-ethyl-2-[4-methoxy-2-(trifluoromethyl)phenyl]-5,6,7a,8,9,10,11,11a-octahydro-4*H*-pyrido[3',4':4,5]pyrrolo[3,2,1-*ij*]quinoline**

30 To a solution of (7a*S*,11a*R*)-2-[4-methoxy-2-(trifluoromethyl)phenyl]-5,6,7a,8,9,10,11,11a-octahydro-4*H*-pyrido[3',4':4,5]pyrrolo[3,2,1-*ij*]quinoline (30 mg, 0.077 mmol) in acetic acid (0.28 mL) was added NaBH₄ (30 mg, 0.80 mmol) in 2 portion in 10 min interval at 55 °C. The reaction mixture was stirred for 15 h at 55 °C then quenched by addition of H₂O. The aqueous solution was basified with 50 %

NaOH then extracted with CHCl₃. The combined organic solution was dried over MgSO₄, concentrated *in vacuo*. The residue was chromatographed (silica gel; CHCl₃: MeOH 99:1-98:2) to give the title compound as a yellow oil (26 mg, 81%). ¹H NMR (CDCl₃, 300 MHz) δ 1.21-1.35 (m, 3H), 2.05-2.30 (m, 5H), 2.53-2.78 (m, 6H), 2.98-3.07 (br, 1H), 3.08-3.18 (br, 1H), 3.27-3.42 (m, 2H), 3.43-3.57 (br, 1H), 3.88 (s, 3H), 6.83 (s, 1H), 6.86 (s, 1H), 7.04 (dd, J = 8.8, 2.9 Hz, 1H), 7.20-7.26 (m, 2H) ppm. MS (CI, NH₃): 417.1 (base, M+H).

EXAMPLE 395

(7a*S*,11a*R*)-2-[4-methoxy-2-(trifluoromethyl)phenyl]-10-propyl-5,6,7a,8,9,10,11,11a-octahydro-4*H*-pyrido[3',4':4,5]pyrrolo[3,2,1-*ij*]quinoline

The title compound was prepared by the method of Example 382 as a yellow oil (23 mg, 69%) from (7a*S*,11a*R*)-2-[4-methoxy-2-(trifluoromethyl)phenyl]-5,6,7a,8,9,10,11,11a-octahydro-4*H*-pyrido[3',4':4,5]pyrrolo[3,2,1-*ij*]quinoline (30 mg, 0.077 mmol) and 1-bromopropane (20 mg, 0.15 mmol). ¹H NMR (CDCl₃, 300 MHz) δ 0.98 (t, J = 7.3 Hz, 3H), 1.78-1.92 (br, 2H), 2.11-2.25 (m, 5H), 2.28-2.42 (m, 1H), 2.53-2.80 (m, 5H), 3.05-3.25 (br, 2H), 3.31 (dt, J = 10.2, 3.6 Hz, 1H), 3.37-3.45 (br, 1H), 3.60-3.72 (br, 1H), 3.89 (s, 3H), 6.85 (s, 1H), 6.87 (s, 1H), 7.05 (dd, J = 8.7, 2.6 Hz, 1H), 7.21-7.27 (m, 2H) ppm. MS (CI, NH₃): 431.2 (base, M+H).

EXAMPLE 396

(7a*S*,11a*R*)-10-butyl-2-[4-methoxy-2-(trifluoromethyl)phenyl]-10-methyl-5,6,7a,8,9,10,11,11a-octahydro-4*H*-pyrido[3',4':4,5]pyrrolo[3,2,1-*ij*]quinoline

The title compound was prepared by the method of Example 382 as a yellow oil (23 mg, 67%) from (7a*S*,11a*R*)-2-[4-methoxy-2-(trifluoromethyl)phenyl]-5,6,7a,8,9,10,11,11a-octahydro-4*H*-pyrido[3',4':4,5]pyrrolo[3,2,1-*ij*]quinoline (30 mg, 0.077 mmol) and 1-bromobutane (21 mg, 0.15 mmol). ¹H NMR (CDCl₃, 300 MHz) δ 0.93 (t, J = 7.3 Hz, 3H), 1.34 (se, J = 7.3 Hz, 2H), 1.65-1.77 (br, 2H), 2.05-2.23 (m, 5H), 2.25-2.38 (br, 1H), 2.55-2.77 (m, 3H), 2.95-3.15 (br, 2H), 3.30 (dt, J =

10.2, 3.7 Hz, 1H), 3.32-3.40 (br, 1H), 3.42-3.55 (br, 1H), 3.86 (s, 3H), 6.82 (s, 1H), 6.85 (s, 1H), 7.03 (dd, $J = 8.8, 2.6$ Hz, 1H), 7.20-7.25 (m, 2H) ppm. MS (CI, NH_3): 445.2 (base, $\text{M}+\text{H}$).

5

EXAMPLE 397

**(7a*S*,11a*R*)-2-[4-methoxy-2-(trifluoromethyl)phenyl]-10-(4-pentenyl)-
5,6,7a,8,9,10,11,11a-octahydro-4*H*-pyrido[3',4':4,5]pyrrolo[3,2,1-*ij*]quinoline**

The title compound was prepared by the method of Example 382 as a yellow
10 oil (22 mg, 63%) from (7a*S*,11a*R*)-2-[4-methoxy-2-(trifluoromethyl)phenyl]-
5,6,7a,8,9,10,11,11a-octahydro-4*H*-pyrido[3',4':4,5]pyrrolo[3,2,1-*ij*]quinoline (30
mg, 0.077 mmol) and 5-bromo-1-pentene (23 mg, 0.15 mmol). ^1H NMR (CDCl_3 ,
300 MHz) δ 1.68-1.79 (m, 2H), 2.01-2.26 (m, 7H), 2.43-2.62 (m, 4H), 2.71 (t, $J = 6.3$
Hz, 2H), 2.83-2.92 (br, 1H), 2.95-3.07 (br, 1H), 3.27-3.44 (m, 3H), 3.86 (s, 3H), 4.93-
15 5.05 (m, 2H), 5.70-5.85 (m, 1H), 6.80 (s, 1H), 6.84 (s, 1H), 7.02 (dd, $J = 8.1, 2.6$ Hz,
1H), 7.18-7.24 (m, 2H) ppm. MS (CI, NH_3): 457.2 (base, $\text{M}+\text{H}$).

EXAMPLE 398

**(7a*S*,11a*R*)-2-[4-methoxy-2-(trifluoromethyl)phenyl]-10-(3-methyl-2-butenyl)-
20 5,6,7a,8,9,10,11,11a-octahydro-4*H*-pyrido[3',4':4,5]pyrrolo[3,2,1-*ij*]quinoline**

The title compound was prepared by the method of Example 382 as a yellow
oil (25 mg, 71%) from (7a*S*,11a*R*)-2-[4-methoxy-2-(trifluoromethyl)phenyl]-
5,6,7a,8,9,10,11,11a-octahydro-4*H*-pyrido[3',4':4,5]pyrrolo[3,2,1-*ij*]quinoline (30
25 mg, 0.077 mmol) and 4-bromo-2-methyl-2-butene (23 mg, 0.15 mmol). ^1H NMR
(CDCl_3 , 300 MHz) δ 1.65 (s, 3H), 1.79 (s, 3H), 2.12-2.22 (m, 3H), 2.24-2.40 (m, 1H),
2.57 (se, $J = 7.7$ Hz, 2H), 2.72 (t, $J = 6.6$ Hz, 2H), 2.74-2.84 (br, 1H), 3.05-3.45 (m,
6H), 3.59-3.77 (m, 1H), 3.86 (s, 3H), 5.42-5.55 (br, 1H), 6.83 (s, 1H), 6.85 (s, 1H),
7.03 (d, $J = 8.8$ Hz, 1H), 7.17-7.25 (m, 2H) ppm. MS (CI, NH_3): 457.2 (base, $\text{M}+\text{H}$).

30

EXAMPLE 399

(7a*S*,11a*R*)-10-(2-fluoroethyl)-2-[4-methoxy-2-(trifluoromethyl)phenyl]-5,6,7a,8,9,10,11,11a-octahydro-4*H*-pyrido[3',4':4,5]pyrrolo[3,2,1-*ij*]quinoline

5 The title compound was prepared by the method of Example 382 as a yellow oil (32 mg, 96%) from (7a*S*,11a*R*)-2-[4-methoxy-2-(trifluoromethyl)phenyl]-5,6,7a,8,9,10,11,11a-octahydro-4*H*-pyrido[3',4':4,5]pyrrolo[3,2,1-*ij*]quinoline (30 mg, 0.077 mmol) and 1-bromo-2-fluoroethane (30 mg, 0.23 mmol). MS (CI, NH₃): 435.1 (base, M+H).

10

EXAMPLE 400

(7a*S*,11a*R*)-10-(2,2-difluoroethyl)-2-[4-methoxy-2-(trifluoromethyl)phenyl]-5,6,7a,8,9,10,11,11a-octahydro-4*H*-pyrido[3',4':4,5]pyrrolo[3,2,1-*ij*]quinoline

15 The title compound was prepared by the method of Example 382 as a yellow oil (27 mg, 77%) from (7a*S*,11a*R*)-2-[4-methoxy-2-(trifluoromethyl)phenyl]-5,6,7a,8,9,10,11,11a-octahydro-4*H*-pyrido[3',4':4,5]pyrrolo[3,2,1-*ij*]quinoline (30 mg, 0.077 mmol) and 2-bromo-1,1-difluoroethane (35 mg, 0.23 mmol). MS (CI, NH₃): 453.1 (base, M+H).

20

EXAMPLE 401

(7a*S*,11a*R*)-10-(cyclobutylmethyl)-2-[4-methoxy-2-(trifluoromethyl)phenyl]-5,6,7a,8,9,10,11,11a-octahydro-4*H*-pyrido[3',4':4,5]pyrrolo[3,2,1-*ij*]quinoline

25 The title compound was prepared by the method of Example 382 as a yellow oil (32 mg, 96%) from (7a*S*,11a*R*)-2-[4-methoxy-2-(trifluoromethyl)phenyl]-5,6,7a,8,9,10,11,11a-octahydro-4*H*-pyrido[3',4':4,5]pyrrolo[3,2,1-*ij*]quinoline (30 mg, 0.077 mmol) and 1-bromo-2-fluoroethane (30 mg, 0.23 mmol). ¹H NMR (CDCl₃, 300 MHz) δ 1.70-1.82 (m, 4H), 1.85-1.98 (m, 1H), 2.02-2.30 (m, 7H), 2.53-
30 2.63 (m, 1H), 2.68-2.88 (m, 5H), 2.92-3.15 (br, 2H), 3.25-3.38 (m, 2H), 3.52-3.62 (br,

1H), 3.87 (s, 3H), 6.82 (s, 1H), 6.84 (s, 1H), 7.03 (dd, J = 8.5, 2.5 Hz, 1H), 7.20-7.25 (m, 2H) ppm. MS (CI, NH₃): 457.2 (base, M+H). MS (CI, NH₃): 457.2 (base, M+H).

EXAMPLE 402

5 **4-((7a*S*,11a*R*)-5,6,8,9,11,11a-hexahydro-4*H*-pyrido[3',4':4,5]pyrrolo[3,2,1-*ij*]quinolin-10(7a*H*)-yl)-1-(4-fluorophenyl)-1-butanone**

To a solution of (7a*S*,11a*R*)-5,6,7a,8,9,10,11,11a-octahydro-4*H*-pyrido[3',4':4,5]pyrrolo[3,2,1-*ij*]quinoline (0.21 g, 1.0 mmol) in 1,4-dioxane (7.0
10 mL) were added 4-chloro-4'-fluorobutyrophenone (0.40 g, 2.0 mmol), KI (catalytic amount) and K₂CO₃ (0.28 g, 2.0 mmol). The reaction mixture was heated at 100 °C for 48 h. The reaction mixture was cooled to 20 °C then diluted with CHCl₃. The solution was filtered to remove excess K₂CO₃ and the filtrate was concentrated *in vacuo* and chromatographed (silica gel, CHCl₃: MeOH 98:2) to give the title
15 compound (0.22 g, 58%) as a white amorphous solid. ¹H NMR (CDCl₃, 300 MHz) δ 1.75-2.20 (m, 7H), 2.20-2.35 (m, 1H), 2.35-2.48 (m, 2H), 2.48-2.60 (m, 1H), 2.60-2.78 (m, 3H), 2.78-2.90 (m, 1H), 2.99 (t, J=7.2 Hz, 2H), 3.05-3.15 (m, 1H), 3.18-3.32 (m, 2H), 6.62 (t, J=7.3 Hz, 1H), 6.86 (d, J=7.3 Hz, 1H), 7.12 (t, J=8.6 Hz, 2H), 7.90-8.08 (m, 2H) ppm.

20

EXAMPLE 403

4-((7a*R*,11a*S*)-5,6,8,9,11,11a-hexahydro-4*H*-pyrido[3',4':4,5]pyrrolo[3,2,1-*ij*]quinolin-10(7a*H*)-yl)-1-(4-fluorophenyl)-1-butanone

25 The title compound (0.16 g, 42%) was prepared by the general method of Example 402 from (7a*R*,11a*S*)-5,6,7a,8,9,10,11,11a-octahydro-4*H*-pyrido[3',4':4,5]pyrrolo[3,2,1-*ij*]quinoline (0.21 g, 1.0 mmol), 4-chloro-4'-fluorobutyrophenone (0.40 g, 2.0 mmol), KI (catalytic) and K₂CO₃ (0.28 g, 2.0 mmol) after chromatographic purification as a white amorphous solid. The ¹H NMR was
30 identical to that of Example 402, 4-((7a*S*,11a*R*)-5,6,8,9,11,11a-hexahydro-4*H*-pyrido[3',4':4,5]pyrrolo[3,2,1-*ij*]quinolin-10(7a*H*)-yl)-1-(4-fluorophenyl)-1-butanone

EXAMPLE 404

4-((7a*S*,11a*R*)-5,6,8,9,11,11a-hexahydro-4*H*-pyrido[3',4':4,5]pyrrolo[3,2,1-*ij*]quinolin-10(7a*H*)-yl)-1-(2-aminophenyl)-1-butanone

5

The title compound (0.031 g, 16%) was prepared by the general method of Example 402 from (7a*S*,11a*R*)-5,6,7a,8,9,10,11,11a-octahydro-4*H*-pyrido[3',4':4,5]pyrrolo[3,2,1-*ij*]quinoline (0.11 g, 0.50 mmol), 4-chloro-2'-aminobutyrophenone (0.20 g, 1.0 mmol), KI (catalytic) and K₂CO₃ (0.14 g, 1.0 mmol) after chromatographic purification as a white amorphous solid. ¹H NMR (CDCl₃, 300 MHz) δ 1.80-2.20 (m, 7H), 2.20-2.60 (m, 3H), 2.82-2.95 (m, 1H), 2.98 (t, J=7.4 Hz, 2H), 3.05-3.20 (m, 2H), 3.20-3.38 (m, 2H), 3.64 (t, J=6.6 Hz, 1H), 3.68-3.80 (m, 1H), 3.81 (t, J=6.0 Hz, 1H), 6.26 (br, 2H), 6.58-6.68 (m, 2H), 6.80-6.92 (m, 2H), 7.10-7.30 (m, 2H), 7.52-7.72 (m, 1H), 7.77 (dd, J=1.3, 8.4 Hz, 1H), 8.09 (td, J=1.6, 8.4 Hz, 1H) ppm.

15

EXAMPLE 405

4-((7a*R*,11a*S*)-5,6,8,9,11,11a-hexahydro-4*H*-pyrido[3',4':4,5]pyrrolo[3,2,1-*ij*]quinolin-10(7a*H*)-yl)-1-(2-aminophenyl)-1-butanone

20

The title compound (0.080 g, 42%) was prepared by the general method of Example 402 from (7a*R*,11a*S*)-5,6,7a,8,9,10,11,11a-octahydro-4*H*-pyrido[3',4':4,5]pyrrolo[3,2,1-*ij*]quinoline (0.11 g, 0.50 mmol), 4-chloro-2'-aminobutyrophenone (0.20 g, 1.0 mmol), KI (catalytic) and K₂CO₃ (0.14 g, 1.0 mmol) after chromatographic purification as a white amorphous solid. The ¹H NMR was identical to that of Example 404, 4-((7a*S*,11a*R*)-5,6,8,9,11,11a-hexahydro-4*H*-pyrido[3',4':4,5]pyrrolo[3,2,1-*ij*]quinolin-10(7a*H*)-yl)-1-(2-aminophenyl)-1-butanone

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EXAMPLE 406

(±)-*cis*-3-(5,6,8,9,11,11a-hexahydro-4*H*-pyrido[3',4':4,5]pyrrolo[3,2,1-*ij*]quinolin-10(7*aH*)-yl)propyl 4-fluorophenyl ether

5 The title compound (0.14 g, 32%) was prepared by the general method of Example 402 from (±)-*cis*-5,6,7a,8,9,10,11,11a-octahydro-4*H*-pyrido[3',4':4,5]pyrrolo[3,2,1-*ij*]quinoline (0.25 g, 1.2 mmol), 1-(3-chloropropoxy)-4-fluorobenzene (0.37 g, 2.0 mmol), KI (catalytic) and K₂CO₃ (0.28 g, 2.0 mmol) after chromatographic purification as a white amorphous solid. ¹H NMR (CDCl₃, 300
10 MHz) δ 1.78-2.08 (m, 7H), 2.10-2.30 (m, 1H), 2.32-2.50 (m, 3H), 2.51-2.72 (m, 3H), 2.75-2.82 (m, 1H), 3.00-3.12 (m, 1H), 3.12-3.25 (m, 2H), 3.89 (t, J=6.3 Hz, 2H), 6.55 (t, J=7.5 Hz, 1H), 6.70-6.92 (m, 6H) ppm.

EXAMPLE 407

15 **4-((±)-*cis*-5,6,8,9,11,11a-hexahydro-4*H*-pyrido[3',4':4,5]pyrrolo[3,2,1-*ij*]quinolin-10(7*aH*)-yl)-1-(4-pyridinyl)-1-butanone**

 The title compound (0.080 g, 18%) was prepared by the general method of Example 402 from (±)-*cis*-5,6,7a,8,9,10,11,11a-octahydro-4*H*-
20 pyrido[3',4':4,5]pyrrolo[3,2,1-*ij*]quinoline (0.25 g, 1.2 mmol), 4-chloro-1-(4-pyridinyl)-1-butanone (0.36 g, 2.0 mmol), KI (catalytic) and K₂CO₃ (0.28 g, 2.0 mmol) after chromatographic purification as a white amorphous solid. ¹H NMR (CDCl₃, 300 MHz) δ 1.68-2.18 (m, 7H), 2.20-2.65 (m, 5H), 2.69 (t, J=6.4 Hz, 2H), 2.72-2.82 (m, 1H), 2.92-3.08 (m, 3H), 3.15-3.28 (m, 2H), 6.62 (t, J=7.5 Hz, 1H), 6.86
25 (d, J=7.6 Hz, 1H), 6.89 (d, J=7.4 Hz, 1H), 7.70-7.80 (m, 2H), 8.75-8.82 (m, 2H) ppm.

EXAMPLE 408**(±)-*cis*-10-[3-(6-fluoro-1,2-benzisoxazol-3-yl)propyl]-5,6,7a,8,9,10,11,11a-octahydro-4*H*-pyrido[3',4':4,5]pyrrolo[3,2,1-*ij*]quinoline**

5 The title compound (0.15 g, 32%) was prepared by the general method of Example 402 from (±)-*cis*-5,6,7a,8,9,10,11,11a-octahydro-4*H*-pyrido[3',4':4,5]pyrrolo[3,2,1-*ij*]quinoline (0.25 g, 1.2 mmol), 3-(3-chloropropyl)-6-fluoro-1,2-benzisoxazole (0.43 g, 2.0 mmol), KI (catalytic) and K₂CO₃ (0.28 g, 2.0 mmol) after chromatographic purification as a white amorphous solid. ¹H NMR
 10 (CDCl₃, 300 MHz) δ 1.80-2.18 (m, 7H), 2.25 (td, J=11.5, 3.0 Hz, 1H), 2.35-2.68 (m, 4H), 2.70 (t, J=6.6 Hz, 2H), 2.75-2.88 (m, 1H), 3.01 (t, J=7.6 Hz, 2H), 3.05-3.15 (m, 1H), 3.20-3.30 (m, 2H), 6.62 (t, J=7.5 Hz, 1H), 6.86 (d, J=7.5 Hz, 1H), 6.92 (d, J=7.5 Hz, 1H), 7.06 (td, J=9.0, 2.1 Hz, 1H), 7.20-7.26 (m, 1H), 7.61 (dd, J=4.8, 8.7 Hz, 1H) ppm.

15

EXAMPLE 409**(7a*S*,11a*R*)-10-[3-(6-fluoro-1,2-benzisoxazol-3-yl)propyl]-5,6,7a,8,9,10,11,11a-octahydro-4*H*-pyrido[3',4':4,5]pyrrolo[3,2,1-*ij*]quinoline**

20 The title compound (0.31 g, 75%) was prepared by the general method of Example 402 from (7a*S*, 11a*R*)-5,6,7a,8,9,10,11,11a-octahydro-4*H*-pyrido[3',4':4,5]pyrrolo[3,2,1-*ij*]quinoline (0.21 g, 1.0 mmol), 3-(3-chloropropyl)-6-fluoro-1,2-benzisoxazole (0.43 g, 2.0 mmol), KI (catalytic) and K₂CO₃ (0.28 g, 2.0 mmol) after chromatographic purification as a white amorphous solid. The ¹H NMR
 25 was identical to that of Example 408, (±)-*cis*-10-[3-(6-fluoro-1,2-benzisoxazol-3-yl)propyl]-5,6,7a,8,9,10,11,11a-octahydro-4*H*-pyrido[3',4':4,5]pyrrolo[3,2,1-*ij*]quinoline

EXAMPLE 410**1-(4-fluorophenyl)-4-(5,6,8,11-tetrahydro-4*H*-pyrido[3',4':4,5]pyrrolo[3,2,1-*ij*]quinolin-10(9*H*)-yl)-1-butanone**

5 The title compound (0.060 g, 28%) was prepared by the general method of Example 402 from 5,6,8,11-tetrahydro-4*H*-pyrido[3',4':4,5]pyrrolo[3,2,1-*ij*]quinoline (0.12 g, 0.57 mmol), 4-chloro-4'-fluorobutyrophenone (0.40 g, 2.0 mmol), KI (catalytic) and K₂CO₃ (0.28 g, 2.0 mmol) after chromatographic purification as a white amorphous solid. ¹H NMR (CDCl₃, 300 MHz) δ 1.80-2.15 (m, 2H), 2.15-2.30 (m, 2H), 2.71 (t, J=7.0 Hz, 2H), 2.82 (d, J=5.1 Hz, 2H), 2.90 (t, J=5.8 Hz, 2H), 2.97 (t, J=6.1 Hz, 2H), 3.02-3.20 (m, 2H), 3.73 (s, 2H), 3.98 (t, J=5.7 Hz, 2H), 6.84 (d, J=6.9 Hz, 1H), 6.97 (t, J=7.5 Hz, 1H), 7.02-7.20 (m, 2H), 7.25 (d, J=7.7 Hz, 1H), 7.20-7.25 (m, 1H), 7.95-8.20 (m, 2H) ppm.

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EXAMPLE 411**(±)-*cis*-4-(4,5,6,7,9,10,12,12a-octahydroazepino[3,2,1-*hi*]pyrido[4,3-*b*]indol-11(8a*H*)-yl)-1-(4-fluorophenyl)-1-butanone**

 The title compound (0.17 g, 74%) was prepared by the general method of Example 402 from (±)-*cis*-4,5,6,7,8a,9,10,11,12,12a-decahydroazepino[3,2,1-*hi*]pyrido[4,3-*b*]indole (0.14 g, 0.59 mmol), 4-chloro-4'-fluorobutyrophenone (0.20 g, 1.0 mmol), KI (catalytic) and K₂CO₃ (0.14 g, 1.0 mmol) after chromatographic purification as a white amorphous solid. ¹H NMR (CDCl₃, 300 MHz) δ 1.42-1.62 (m, 1H), 1.62-1.80 (m, 1H), 1.88-2.22 (m, 7H), 2.40-2.70 (m, 5H), 2.80-3.12 (m, 5H), 3.12-3.30 (m, 2H), 3.32-3.50 (m, 1H), 6.69 (t, J=7.5 Hz, 1H), 6.80-7.00 (m, 2H), 7.05-7.20 (m, 2H), 7.90-8.03 (m, 2H) ppm.

EXAMPLE 412

4-((8a*S*,12a*R*)-4,5,6,7,9,10,12,12a-octahydroazepino[3,2,1-*hi*]pyrido[4,3-*b*]indol-11(8a*H*)-yl)-1-(4-fluorophenyl)-1-butanone

5 The title compound was prepared by preparative HPLC separation of (±)-*cis*-4-(4,5,6,7,9,10,12,12a-octahydroazepino[3,2,1-*hi*]pyrido[4,3-*b*]indol-11(8a*H*)-yl)-1-(4-fluorophenyl)-1-butanone on a CHIRALPAK® AD column (CH₃CN/Ethanol/DEA = 85/15/0.05).

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EXAMPLE 413

4-((8a*R*,12a*S*)-4,5,6,7,9,10,12,12a-octahydroazepino[3,2,1-*hi*]pyrido[4,3-*b*]indol-11(8a*H*)-yl)-1-(4-fluorophenyl)-1-butanone

15 The title compound was prepared by preparative HPLC separation of (±)-*cis*-4-(4,5,6,7,9,10,12,12a-octahydroazepino[3,2,1-*hi*]pyrido[4,3-*b*]indol-11(8a*H*)-yl)-1-(4-fluorophenyl)-1-butanone on a CHIRALPAK® AD column (CH₃CN/Ethanol/DEA = 85/15/0.05).

EXAMPLE 414

20 **4-((±)-4,5,6,7,9,10,12,12a-octahydroazepino[3,2,1-*hi*]pyrido[4,3-*b*]indol-11(8a*H*)-yl)-1-(2-amino-4-fluorophenyl)-1-butanone**

25 The title compound (0.16 g, 67%) was prepared by the general method of Example 402 from (±)-*cis*-4,5,6,7,8a,9,10,11,12,12a-decahydroazepino[3,2,1-*hi*]pyrido[4,3-*b*]indole (0.14 g, 0.59 mmol), 4-chloro-2'-amino-4'-fluorobutyrophenone (0.22 g, 1.0 mmol), KI (catalytic) and K₂CO₃ (0.14 g, 1.0 mmol) after chromatographic purification as a white amorphous solid. ¹H NMR (CDCl₃, 300 MHz) δ 1.45-1.62 (m, 2H), 1.62-2.10 (m, 8H), 2.20-2.52 (m, 4H), 2.52-2.72 (m, 2H), 2.72-2.84 (m, 1H), 2.84-3.00 (m, 2H), 3.12-3.30 (m, 3H), 6.20-6.60 (m, 4H),
30 6.67 (t, J=7.3 Hz, 1H), 6.91 (t, J=7.7 Hz, 2H), 7.77 (dd, J=6.4, 9.0 Hz, 1H) ppm.

EXAMPLE 415**4-((±)-*cis*-5,6,8,9,11,11a-hexahydro-4*H*-pyrido[3',4':4,5]pyrrolo[3,2,1-*ij*]quinolin-10(7a*H*)-yl)-1-(2-amino-4-fluorophenyl)-1-butanone**

5 The title compound was prepared by the method of Example 402 as a red oil (99 mg, 54%) from (±)-*cis*-5,6,7a,8,9,10,11,11a-octahydro-4*H*-pyrido[3',4':4,5]pyrrolo[3,2,1-*ij*]quinoline (100 mg, 0.47 mmol) and 1-(2-amino-4-fluorophenyl)-4-chloro-1-butanone (152 mg, 0.70 mmol). ¹H NMR (CDCl₃, 300 MHz) δ 1.95-2.15 (m, 7H), 2.37-2.57 (m, 5H), 2.67-2.85 (m, 3H), 2.90-3.05 (m, 3H),
10 3.24-3.33 (m, 2H), 6.27-6.39 (m, 2H), 6.41-6.50 (br, 2H), 6.64 (t, J = 7.3 Hz, 1H), 6.85-6.94 (m, 2H), 7.77 (dd, J = 9.2, 6.6 Hz, 1H) ppm.

EXAMPLE 416**4-((7a*S*,11a*R*)-5,6,8,9,11,11a-hexahydro-4*H*-pyrido[3',4':4,5]pyrrolo[3,2,1-*ij*]quinolin-10(7a*H*)-yl)-1-(2-amino-4-fluorophenyl)-1-butanone**

15 The title compound was prepared by the method of Example 402 as a yellow oil (35 mg, 20%) from (7a*S*,11a*R*)-5,6,7a,8,9,10,11,11a-octahydro-4*H*-pyrido[3',4':4,5]pyrrolo[3,2,1-*ij*]quinoline (100 mg, 0.47 mmol) and 1-(2-amino-4-fluorophenyl)-4-chloro-1-butanone (202 mg, 0.93 mmol). The title compound was
20 spectroscopically identical to Example 415.

EXAMPLE 417**4-((7a*R*,11a*S*)-5,6,8,9,11,11a-hexahydro-4*H*-pyrido[3',4':4,5]pyrrolo[3,2,1-*ij*]quinolin-10(7a*H*)-yl)-1-(2-amino-4-fluorophenyl)-1-butanone**

25 The title compound was prepared by the method of Example 402 as a yellow oil (95 mg, 34%) from (7a*R*,11a*S*)-5,6,7a,8,9,10,11,11a-octahydro-4*H*-pyrido[3',4':4,5]pyrrolo[3,2,1-*ij*]quinoline (150 mg, 0.70 mmol) and 1-(2-amino-4-fluorophenyl)-4-chloro-1-butanone (303 mg, 1.40 mmol). The title compound was
30 spectroscopically identical to Example 415.

EXAMPLE 418

5,6,9,10,11,12-hexahydro-4*H*,8*H*-azepino[4',5':4,5]pyrrolo[3,2,1-*ij*]quinoline

5 To a solution of 3,4-dihydro-1(2*H*)-quinolinamine (1.0 g, 14 mmol) and hexahydro-4*H*-azepin-4-one hydrochloride (1.0 g, 14 mmol) in EtOH (13 mL) was added concentrated HCl (1.2 mL). The reaction was stirred at reflux for 14 h, then cooled to 20 °C. A brown precipitate was filtered from the reaction mixture, affording the title compound (800 mg, 45%) as a brown solid. ¹H NMR (CD₃OD, 10 300 MHz) δ 2.14-2.23 (m, 2H), 2.91 (t, 2H, *J* = 6.0 Hz), 3.16-3.21 (m, 2H), 3.27-3.33 (m, 2H), 3.39-3.50 (m, 4H), 4.04 (t, 2H, *J* = 5.7 Hz), 6.70 (d, 1H, *J* = 6.9 Hz), 6.87-6.93 (m, 1H), 7.22 (d, 1H, *J* = 8.0 Hz) ppm. MS (ESI): 227.2 (base, *M* + *H*).

EXAMPLE 419

15 **(±)-5,6,8,9,10,11,12,12a-octahydro-4*H*,7a*H*-azepino[4',5':4,5]pyrrolo[3,2,1-*ij*]quinoline**

Step A:

To a solution of 5,6,9,10,11,12-hexahydro-4*H*,8*H*-azepino[4',5':4,5]pyrrolo[3,2,1-*ij*]quinoline (150 mg, 0.65 mmol) in TFA (7.5 mL) 20 was added NaCNBH₃ (123 mg, 1.95 mmol) in small portions at 0 °C. The reaction mixture was stirred for 1 h. To the reaction mixture was added concentrated HCl (5 mL) and the reaction was heated at reflux for 10 m. The reaction mixture was concentrated *in vacuo* and basified to pH 14 with 50% NaOH. To this was added 1,4- 25 dioxane (14 mL), and to this solution was added di-*tert*-butyl dicarbonate (700 mg, 3.2 mmol). The solution was stirred at 20 °C for 16 h. Purification by column chromatography (hexanes:EtOAc 19:1) afforded *tert*-butyl (±)-5,6,8,9,10,11,12,12a-octahydro-4*H*,7a*H*-azepino[4',5':4,5]pyrrolo[3,2,1-*ij*]quinoline-10-carboxylate as a colorless oil.

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Step B:

To a solution of *tert*-butyl (±)-5,6,8,9,10,11,12,12a-octahydro-4*H*,7*aH*-azepino[4',5':4,5]pyrrolo[3,2,1-*ij*]quinoline-10-carboxylate in CH₂Cl₂ (2.4 mL) was added TFA (0.6 mL). This was stirred at 20 °C for 3 h. The reaction mixture was diluted with CH₂Cl₂ (50 mL) and washed with saturated NaHCO₃ (50 mL) and brine (50 mL), dried over MgSO₄ and concentrated *in vacuo* to afford the title compound as a yellow oil (87 mg, 59%). ¹H NMR (CDCl₃, 300 MHz) δ 1.77-2.13 (m, 7H), 2.56-2.79 (m, 5H), 2.83-2.93 (m, 1H), 3.00-3.16 (m, 2H), 3.33-3.41 (td, 1H, *J* = 3.7, 9.2 Hz), 3.60 (td, 1H, *J* = 4.4, 9.1 Hz), 6.50 (t, 1H, *J* = 7.3 Hz), 6.76 (t, 2H, 8.0 Hz) ppm.

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EXAMPLE 420

4-[(±)-5,6,8,9,10,11,12,12a-octahydro-4*H*,7*aH*-azepino[4',5':4,5]pyrrolo [3,2,1-*ij*]quinolin-10-yl]-1-(4-fluorophenyl)-1-butanone

The title compound was isolated as a yellow oil (55 mg, 37%) according to the method of Example 402 from (±)-5,6,8,9,10,11,12,12a-octahydro-4*H*,7*aH*-azepino[4',5':4,5]pyrrolo[3,2,1-*ij*]quinoline (87mg, 0.38 mmol) and 4-chloro-1-(4-fluorophenyl)-1-butanone (153 mg, 0.76 mmol). ¹H NMR (CDCl₃, 300 MHz) δ 2.04-2.36 (m, 6H), 2.65-2.89 (m, 6H), 2.93-3.39 (m, 8H), 3.50-3.59 (m, 1H), 3.71-3.80 (m, 1H), 6.65 (t, 1H, *J* = 7.3 Hz), 6.87 (t, 2H, *J* = 6.9 Hz), 7.09-7.17 (m, 2H), 7.94-8.01 (m, 2H) ppm.

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EXAMPLE 421

4-[(±)-5,6,8,9,10,11,12,12a-octahydro-4*H*,7*aH*-azepino[4',5':4,5]pyrrolo [3,2,1-*ij*]quinolin-10-yl]-1-(2-amino-4-fluorophenyl)-1-butanone

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The title compound was isolated as a yellow oil (23 mg, 12%) according to the method of Example 402 from (±)-5,6,8,9,10,11,12,12a-octahydro-4*H*,7*aH*-azepino[4',5':4,5]pyrrolo[3,2,1-*ij*]quinoline (111 mg, 0.49 mmol) and 4-chloro-1-(2-amino-4-fluorophenyl)-1-butanone (210 mg, 0.97 mmol). ¹H NMR (CDCl₃, 300 MHz) δ 1.98-2.11 (m, 5H), 2.38-2.57 (m, 2H), 2.60-2.69 (m, 3H), 2.71-3.13 (m,

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10H), 3.39-3.47 (m, 1H), 3.63-3.70 (m, 1H), 6.20-6.41 (m, 4H), 6.56 (t, 1H, $J = 7.3$ Hz), 6.79 (d, 2H, 7.7 Hz), 7.63-7.69 (m, 1H) ppm.

EXAMPLE 4225 **4,5,6,9,10,11,12,13-octahydro-9*H*-diazepino[4,5-*b*:3,2,1-*hi*]indole**

The title compound was prepared as a brown solid (287 mg, 65%) according to the method of Example 418 from 2,3,4,5-tetrahydro-1*H*-1-benzazepin-1-amine (300 mg, 1.85 mmol) and hexahydro-4*H*-azepin-4-one hydrochloride (277 mg, 1.85 mmol). ¹H NMR (CD₃OD, 300 MHz) δ 1.99-2.16 (m, 4H), 3.04-3.12 (m, 5H), 3.16-3.21 (m, 2), 3.32-3.41 (m, 3H), 4.09-4.15 (m, 2H), 6.80-6.91 (m, 2H), 7.22 (d, 1H, $J = 6.9$ Hz) ppm.

EXAMPLE 42315 **(\pm)-4,5,6,7,9,10,11,12,13,13a-decahydro-8a*H*-diazepino[4,5-*b*:3,2,1-*hi*]indole**

The title compound was isolated as a yellow oil (38 mg, 25%) according to the procedure of Example 419, Steps A and B from 4,5,6,9,10,11,12,13-octahydro-9*H*-diazepino[4,5-*b*:3,2,1-*hi*]indole (152 mg, 0.63 mmol). ¹H NMR (CDCl₃, 300 MHz) δ 1.37-1.55 (m, 1H), 1.64-1.80 (m, 1H), 1.85-2.09 (m, 4H), 2.11-2.23 (m, 2H), 2.56-2.97 (m, 6H), 3.12-3.23 (m, 2H), 3.57-3.71 (m, 2H), 6.68 (t, 1H, $J = 7.4$ Hz), 6.87-6.91 (m, 2H) ppm.

EXAMPLE 42425 **4-[(\pm)-4,5,6,7,9,10,11,12,13,13a-decahydro-11*H*-diazepino[4,5-*b*:3,2,1-*hi*]indol-11-yl]-1-(4-fluorophenyl)-1-butanone**

The title compound was isolated as a yellow oil (20 mg, 60%) according to the method of Example 402 from (\pm)-4,5,6,7,9,10,11,12,13,13a-decahydro-8a*H*-diazepino[4,5-*b*:3,2,1-*hi*]indole (20 mg, 0.08 mmol) and 4-chloro-1-(4-fluorophenyl)-1-butanone (32 mg, 0.16 mmol). ¹H NMR (CDCl₃, 300 MHz) δ 1.37-1.45 (m, 1H),

1.59-1.77 (m, 1H), 1.91-2.04 (m, 6H), 2.13-2.22 (m, 2H), 2.55-2.71 (m, 6H), 2.85-3.19 (m, 6H), 3.53-3.67 (m, 2H), 6.68 (t, 1H, $J = 7.3$ Hz), 6.88 (d, 2H, $J = 7.3$ Hz), 7.08-7.16 (m, 2H), 7.97-8.03 (m, 2H) ppm.

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EXAMPLE 425

4-[(±)-4,5,6,7,9,10,11,12,13,13a-decahydro-11*H*-diazepino[4,5-*b*:3,2,1-*hi*]indol-11-yl]-1-(2-amino-4-fluorophenyl)-1-butanone

The title compound was isolated as a yellow oil (23 mg, 66%) according to the method of Example 402 from (±)-4,5,6,7,9,10,11,12,13,13a-decahydro-8a*H*-diazepino[4,5-*b*:3,2,1-*hi*]indole (20 mg, 0.08 mmol) and 4-chloro-1-(2-amino-4-fluorophenyl)-1-butanone (53 mg, 0.25 mmol). ¹H NMR (CDCl₃, 300 MHz) δ 1.30-1.43 (m, 1H), 1.53-1.64 (m, 1H), 1.88-2.01 (m, 6H), 2.10-2.22 (m, 2H), 2.50-2.70 (m, 6H), 2.70-3.09 (m, 6H), 3.26-3.44 (m, 2H), 6.20-6.30 (m, 2H), 6.36 (br, 2H), 6.62 (t, 1H, $J = 7.4$ Hz), 6.79-6.85 (m, 2H), 7.65-7.70 (m, 1H) ppm.

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EXAMPLE 426

(±)-*cis*-6,7,8a,9,10,11,12,12a-octahydroazepino[3,2,1-*hi*]pyrido[4,3-*b*]indol-4(5*H*)-one

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Step A:

To a stirred solution of 1M BCl₃ in toluene (8.8 mL, 8.8 mmol) was added ethyl (±)-*cis*-1,3,4,4a,5,9b-hexahydro-2*H*-pyrido[4,3-*b*]indole-2-carboxylate (984 mg, 4.0 mmol) in benzene (32 mL) at 0°C. To the above solution was added 4-chlorobutanenitrile (0.39 mL, 4.4 mmol), and AlCl₃ (587 mg, 4.4 mmol), the reaction mixture was stirred at r.t. for 10 min., then was heated in a sealed tube for 18 h. After cooled down to r.t., was added 5N HCl (32 mL) and heated at 80°C for 30 min. The reaction mixture was neutralized by 50% NaOH at 0°C, adjusted pH=14, extracted with CH₂Cl₂ (200 mL), the organic layer was dried over MgSO₄, and concentrated *in vacuo* to afford after chromatographic purification ethyl (±)-*cis*-6-(4-

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chlorobutanoyl)-1,3,4,4a,5,9b-hexahydro-2*H*-pyrido[4,3-*b*]indole-2-carboxylate (413mg, 30%).

Step B:

5 To ethyl (±)-*cis*-6-(4-chlorobutanoyl)-1,3,4,4a,5,9b-hexahydro-2*H*-pyrido[4,3-*b*]indole-2-carboxylate (100mg, 0.29 mmol) in butanol (3 mL) was added KOH(50 mg) and heated at 109°C for 5hr.. After cooled down to r.t., KOH(50 mg) and KI(20 mg) were added. The reaction mixture was heated at 109°C in a sealed tube for 18 h. The reaction mixture was cooled down to r.t., extracted with CH₂Cl₂, dried over
10 MgSO₄ to afford (±)-*cis*-6,7,8a,9,10,11,12,12a-octahydroazepino[3,2,1-*hi*]pyrido[4,3-*b*]indol-4(5*H*)-one (69 mg, 99%).

Step C:

To (±)-*cis*-6,7,8a,9,10,11,12,12a-octahydroazepino[3,2,1-*hi*]pyrido[4,3-*b*]indol-4(5*H*)-one (61mg, 0.25 mmol) in dioxane(1 mL) and 1N NaOH (1 mL) was
15 added Boc₂O (60 mg, 0.27mmol), stirred at r.t. for 18 h. After extracted with CH₂Cl₂, dried over MgSO₄, concentrated *in vacuo* to afford *tert*-butyl (±)-*cis*-4-oxo-4,5,6,7,9,10,12,12a-octahydroazepino[3,2,1-*hi*]pyrido[4,3-*b*]indole-11(8a*H*)-carboxylate (40mg, 47%).

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Step D:

The title compound was prepared by the method of Example 98 from *tert*-butyl (±)-*cis*-4-oxo-4,5,6,7,9,10,12,12a-octahydroazepino[3,2,1-*hi*]pyrido[4,3-*b*]indole-11(8a*H*)-carboxylate to afford the title compound (25mg, 88%). ¹H NMR
25 (CD₃OD, 300 MHz) δ 7.86-7.89(m, 1H), 7.34(d, 1H, 6.9Hz), 6.73-6.78(m, 1H), 4.02-4.04(m, 1H), 3.37-3.39(m, 2H), 3.20-3.27(m, 2H), 2.82-2.92(m, 1H), 2.74-2.80(m, 1H), 2.10-2.14(m, 2H), 0.94-1.07(m, 5H) ppm. MS – ESI: 243 [MH]⁺.

EXAMPLE 427

***tert*-butyl (±)-*cis*-2-bromo-4-oxo-4,5,6,7,9,10,12,12a-octahydroazepino[3,2,1-*hi*]pyrido[4,3-*b*]indole-11(8a*H*)-carboxylate**

5 The title compound was prepared by the method of Example 89 step B from *tert*-butyl (±)-*cis*-4-oxo-4,5,6,7,9,10,12,12a-octahydroazepino[3,2,1-*hi*]pyrido[4,3-*b*]indole-11(8a*H*)-carboxylate (88mg, 0.26 mmol) to afford the title compound (110mg, 100%).

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EXAMPLE 428

***tert*-butyl (±)-*cis*-2-(2,4-dichlorophenyl)-4-oxo-4,5,6,7,9,10,12,12a-octahydroazepino[3,2,1-*hi*]pyrido[4,3-*b*]indole-11(8a*H*)-carboxylate**

15 The title compound was prepared by the method of Example 89 step C from *tert*-butyl (±)-*cis*-2-bromo-4-oxo-4,5,6,7,9,10,12,12a-octahydroazepino[3,2,1-*hi*]pyrido[4,3-*b*]indole-11(8a*H*)-carboxylate (110mg, 0.26 mmol) and corresponding 2,4-dichlorophenylboronic acid (60mg, 0.31 mmol) to afford after chromatographic purification the title compound (70mg, 55%).

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EXAMPLE 429

(±)-*cis*-2-(2,4-dichlorophenyl)-6,7,8a,9,10,11,12,12a-octahydroazepino[3,2,1-*hi*]pyrido[4,3-*b*]indol-4(5*H*)-one

25 The title compound was prepared by the method of Example 98 from *tert*-butyl (±)-*cis*-2-(2,4-dichlorophenyl)-4-oxo-4,5,6,7,9,10,12,12a-octahydroazepino[3,2,1-*hi*]pyrido[4,3-*b*]indole-11(8a*H*)-carboxylate to afford the title compound (50mg, 90%). ¹H NMR (CD₃OD, 300 MHz) δ 7.78(d, 1H, 1.4Hz), 7.48(d, 1H, 1.9Hz), 7.28-7.32(m, 2H), 7.01(s, 1H), 4.06-4.12(m, 1H), 2.59-3.22(m, 6H), 1.71-2.04(m, 3H), 0.95-1.28(m, 4H) ppm. MS – ApCI: 387 [M+H⁺].

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EXAMPLE 430

(8a*S*, 12a*R*)-2-(2,4-dichlorophenyl)-6,7,8a,9,10,11,12,12a-octahydroazepino[3,2,1-*hi*]pyrido[4,3-*b*]indol-4(5*H*)-one

5 The resolution of 2-(2,4-dichlorophenyl)-6,7,8a,9,10,11,12,12a-octahydroazepino[3,2,1-*hi*]pyrido[4,3-*b*]indol-4(5*H*)-one was carried out by High Performance Liquid Chromatography using a chiral column to afford the title compound.

EXAMPLE 431

10 **(8a*R*, 12a*S*)-2-(2,4-dichlorophenyl)-6,7,8a,9,10,11,12,12a-octahydroazepino[3,2,1-*hi*]pyrido[4,3-*b*]indol-4(5*H*)-one**

15 The resolution of 2-(2,4-dichlorophenyl)-6,7,8a,9,10,11,12,12a-octahydroazepino[3,2,1-*hi*]pyrido[4,3-*b*]indol-4(5*H*)-one was carried out by High Performance Liquid Chromatography using a chiral column to afford the title compound.

EXAMPLE 432

20 **(8a*S*, 12a*R*)-2-(2,4-dichlorophenyl)-6,7,8a,9,10,11,12,12a-decahydroazepino[3,2,1-*hi*]pyrido[4,3-*b*]indol-4-ol**

25 To (8a*S*, 12a*R*)-2-(2,4-dichlorophenyl)-6,7,8a,9,10,11,12,12a-octahydroazepino[3,2,1-*hi*]pyrido[4,3-*b*]indol-4(5*H*)-one (12 mg, 0.03 mmol) in CH₃OH(1 mL) at RT was added NaBH₄ (5.4mg, 0.15 mmol) in three portions. The reaction mixture was stirred at RT for 2 h 2 drops of 1N HCl were added to the reaction mixture, concentrated *in vacuo*. NH₄OH (1 mL) and water (2 mL) were added, extracted with CH₂Cl₂ (3 x 3 mL). The combined organic layer was dried over MgSO₄, concentrated to afford the title compound (8mg, 69%). MS – ESI: 389 [MH]
30 +.

EXAMPLE 433**(8a*R*, 12a*S*)-2-(2,4-dichlorophenyl)-6,7,8a,9,10,11,12,12a-decahydroazepino[3,2,1-*hi*]pyrido[4,3-*b*]indol-4-ol**

5 The title compound was prepared by the method of Example 432 from (8a*R*, 12a*S*)-2-(2,4-dichlorophenyl)-6,7,8a,9,10,11,12,12a-octahydroazepino[3,2,1-*hi*]pyrido[4,3-*b*]indol-4(5*H*)-one (14 mg, 0.04 mmol) to afford the title compound (12mg, 86%). MS – ESI: 389 [MH]⁺.

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EXAMPLE 434**(±)-*cis*-5,6,8,9,10,11,12,12a-octahydro-4*H*,7a*H*-azepino[3',4':4,5]pyrrolo[3,2,1-*ij*]quinoline****Step A:**

15 3,4-Dihydro-1(2*H*)-quinolinamine hydrochloride (5.0 g, 27 mmol) and 1,3-cyclohexanedione (3.1 g, 27 mmol) was mixed in AcOH (4.3 mL) and H₂O (4.3 mL). The mixture was heated at 40 °C for 10 min until dissolved completely. The mixture was then concentrated to dryness. The residue was washed with acetonitrile then filtered to yield 3-(3,4-dihydro-1(2*H*)-quinolinylimino)-1-cyclohexen-1-ol
20 hydrochloride (5.2 g, 69 %) as a yellow solid.

Step B:

 3-(3,4-Dihydro-1(2*H*)-quinolinylimino)-1-cyclohexen-1-ol hydrochloride (4.78 g, 17 mmol) was mixed with AcOH (37 mL) and conc. HCl (6.1 mL). The
25 reaction mixture was refluxed for 1h and cooled to RT. The reaction mixture was concentrated *in vacuo* then the residue was dissolved in CH₂Cl₂. The organic solution was washed with H₂O and brine, dried over MgSO₄, filtered and concentrated *in vacuo*. The residue was chromatographed in silica gel (hex:EtOAc 1:1) to give 5,6,9,10-tetrahydro-4*H*-pyrido[3,2,1-*jk*]carbazol-11(8*H*)-one (1.25 g,
30 33%) as a light yellow solid.

Step C:

To a solution of 5,6,9,10-tetrahydro-4*H*-pyrido[3,2,1-*jk*]carbazol-11(8*H*)-one (820 mg, 3.6 mmol) in ethanol (7.5 mL) and H₂O (3.6 mL) was added hydroxylamine hydrochloride (380 mg, 5.5 mmol) and sodium acetate (452 mg, 5.5 mmol). The
 5 reaction mixture was refluxed for 15h then cooled to RT.

The precipitated solid was filtered and washed with H₂O. The solid was dried under vacuum to give 5,6,9,10-tetrahydro-4*H*-pyrido[3,2,1-*jk*]carbazol-11(8*H*)-one oxime (824 mg, 95%) as a gray powder.

10 **Step D:**

To a preheated polyphosphoric acid (25 g) was added 5,6,9,10-tetrahydro-4*H*-pyrido[3,2,1-*jk*]carbazol-11(8*H*)-one oxime (810 mg, 3.3 mmol) in one portion at 110 °C. The reaction mixture was stirred for 30 min at the same temperature then pour
 15 into ice water (100 mL) and triturated to complete the dissolution of the polyphosphoric acid. After 1h stirring at 20 °C, gummy solid was formed, and it was washed with H₂O and NH₄OH. The solid was crystallized in EtOAc to give 5,6,8,9,10,11-hexahydro-4*H*,12*H*-azepino[3',4':4,5]pyrrolo[3,2,1-*ij*]quinolin-12-one (320 mg, 40%) as a yellow solid.

20 **Step E:**

To a suspension of LiAlH₄ in 1,4-dioxane (26 mL) was added 5,6,8,9,10,11-hexahydro-4*H*,12*H*-azepino[3',4':4,5]pyrrolo[3,2,1-*ij*]quinolin-12-one (300 mg, 1.25 mmol) under N₂ at 20 °C. The reaction mixture was refluxed for 15 h. The reaction mixture was cooled in an ice bath and added successively with H₂O (0.3 mL), 15%
 25 NaOH (0.3 mL) and H₂O (0,8 mL). The mixture was stirred for 1h at 20°C then filtered. The filtrate was concentrated *in vacuo*. The residue was dissolved in dilute AcOH and washed with Et₂O. The aqueous solution was basified with 1N NaOH. A white solid was precipitated and filtered to yield 5,6,9,10,11,12-hexahydro-4*H*,8*H*-azepino[3',4':4,5]pyrrolo[3,2,1-*ij*]quinoline (270 mg, 95%).

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Step F:

To a solution of 5,6,9,10,11,12-hexahydro-4*H*,8*H*-azepino[3',4':4,5]pyrrolo[3,2,1-*ij*]quinoline (240 mg, 1.06 mmol) in TFA (4.0 mL) was added Et₃SiH (2.0 mL). The mixture was stirred for 3 days then concentrated *in vacuo*. The residue was dissolved in dilute AcOH and washed with Et₂O. The aqueous solution was basified with 1N NaOH. A white solid was precipitated and filtered to yield the title compound as a pale yellow viscous oil (200 mg, 83%). MS (CI, NH₃): 229.4 (base, M+H).

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EXAMPLE 435

***tert*-butyl (±)-*cis*-5,6,8,9,10,11,12,12a-octahydro-4*H*,7a*H*-azepino[3',4':4,5]pyrrolo[3,2,1-*ij*]quinoline-11-carboxylate**

The title compound (114 mg, 99%) was prepared by the method of Example 311 from (±)-*cis*-5,6,8,9,10,11,12,12a-octahydro-4*H*,7a*H*-azepino[3',4':4,5]pyrrolo[3,2,1-*ij*]quinoline (80 mg, 0.35 mmol) as a viscous colorless oil. MS (ESI): 329.4 (base, M+H).

EXAMPLE 436

***tert*-butyl (±)-*cis*-2-bromo-5,6,8,9,10,11,12,12a-octahydro-4*H*,7a*H*-azepino[3',4':4,5]pyrrolo[3,2,1-*ij*]quinoline-11-carboxylate**

The title compound (120 mg, 81%) was prepared by the method of Example 314 from *tert*-butyl (±)-*cis*-5,6,8,9,10,11,12,12a-octahydro-4*H*,7a*H*-azepino[3',4':4,5]pyrrolo[3,2,1-*ij*]quinoline (114 mg, 0.35 mmol) as a viscous colorless oil.

EXAMPLE 437

(±)-*cis*-2-[4-methoxy-2-(trifluoromethyl)phenyl]-5,6,8,9,10,11,12,12a-octahydro-4*H*,7*aH*-azepino[3',4':4,5]pyrrolo[3,2,1-*ij*]quinoline

5 **Step A:**

Tert-butyl (±)-*cis*-2-[4-methoxy-2-(trifluoromethyl)phenyl]-5,6,8,9,10,11,12,12a-octahydro-4*H*,7*aH*-azepino[3',4':4,5]pyrrolo[3,2,1-*ij*]quinoline-11-carboxylate (56 mg, 91%) was prepared by the general method of Example 319, step A from *tert*-butyl (±)-*cis*-2-bromo-5,6,8,9,10,11,12,12a-octahydro-4*H*,7*aH*-azepino[3',4':4,5]pyrrolo[3,2,1-*ij*]quinoline-11-carboxylate (50 mg, 0.12 mmol) and 4-methoxy-2-(trifluoromethyl)phenylboronic acid (54 mg, 0.25 mmol) as a white foam. MS (ESI): 503.6 (base, M+H).

Step B:

15 The title compound (44 mg, 99%) was prepared by the general method of Example 312, step B from *tert*-Butyl (±)-*cis*-2-[4-methoxy-2-(trifluoromethyl)phenyl]-5,6,8,9,10,11,12,12a-octahydro-4*H*,7*aH*-azepino[3',4':4,5]pyrrolo[3,2,1-*ij*]quinoline-11-carboxylate (54 mg, 0.11 mmol) as a white foam. MS (CI): 403.4 (base, M+H).

20

UTILITY

The compounds of the present invention have therapeutic utility for illnesses or disorders involving the neurotransmitter serotonin (5-hydroxy tryptamine or 5-HT) and either agonism or antagonism of 5-HT₂ receptors, as demonstrated by the assays described below. Therapeutic utility for these illnesses or disorders could involve numerous biological processes affected by serotonin including, but not limited to, appetite, mood, sleep, sexual activity, and arterial constriction. These biological processes may also be important to numerous central nervous system (CNS) disorders including those related to the affective disorders of depression, anxiety, psychosis, and schizophrenia, as well as, disorders of food intake such as anorexia, bulimia, and obesity. The compounds of the present invention potentially have therapeutic utility

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in other conditions in which serotonin has been implicated, such as migraine, attention deficit disorder or attention deficit hyperactivity disorder, addictive behavior, and obsessive-compulsive disorder, as well as, conditions associated with cephalic pain, social phobias, and gastrointestinal disorders such as dysfunction of the gastrointestinal tract motility. Lastly, compounds of the present invention potentially have therapeutic utility in neurodegenerative diseases and traumatic conditions represented by the examples of Alzheimer's disease and brain/spinal cord trauma.

The pharmacological analysis of each compound for either antagonism or agonism of at 5-HT_{2A} and 5-HT_{2C} receptors consisted of in vitro and in vivo studies. In vitro analyses included K_i determinations at 5-HT_{2A} and 5-HT_{2C} receptors and an assessment of functional (i.e., agonism or antagonism) activity at each receptor class by IP₃ hydrolysis assays. Additional receptor assays were conducted to evaluate receptor specificity of 5-HT_{2A} and 5-HT_{2C} receptors over monoamine and nuisance receptors (e.g. histamine, dopamine, and muscarinic). A compound is considered active as a 5-HT_{2A} antagonist or a 5-HT_{2C} agonist if it has an IC₅₀ value or a K_i value of less than about 1 micromolar; preferably less than about 0.1 micromolar; more preferably less than about 0.01 micromolar. Compounds of the invention have been shown to have an IC₅₀ value of less than about 1 micromolar for 5-HT_{2A} antagonism or a 5-HT_{2C} agonism.

In vivo assays assessed compound activity in a variety of behavioral paradigms including quipazine head twitch, acute and chronic feeding models, anxiety and depression models (learned-helplessness, elevated plus maze, Geller-Siefter, conditioned taste aversion, taste reactivity, satiety sequence). In aggregate, these models reflect activity as a 5-HT_{2A} antagonist (quipazine head twitch, depression models) or 5-HT_{2C} agonist (feeding models, anxiety models, depression models) and provide some indication as to bioavailability, metabolism and pharmacokinetics.

Radioligand binding experiments were conducted on recombinant human 5-HT_{2A} and 5-HT_{2C} receptors expressed in HEK293E cells. The affinities of compounds of the present invention to bind at these receptors is determined by their capacity to compete for [¹²⁵I]-1-(2,5-dimethoxy-4-iodophenyl)-2-amino-propane (DOI) binding at the 5-HT_{2A} or 5-HT_{2C}. General references for binding assays

include 1) Lucaites VL, Nelson DL, Wainscott DB, Baez M (1996) Receptor subtype and density determine the coupling repertoire of the 5-HT₂ receptor subfamily. *Life Sci.*, 59(13):1081-95. *J Med Chem* 1988 Jan;31(1):5-7; 2) Glennon RA, Seggel MR, Soine WH, Herrick-Davis K, Lyon RA, Titeler M (1988) [125I]-1-(2,5-dimethoxy-4-iodophenyl)-2-amino-propane: an iodinated radioligand that specifically labels the agonist high-affinity state of 5-HT₂ serotonin receptors. *J Med. Chem.* 31(1):5-7 and 3) Leonhardt S, Gorospe E, Hoffman BJ, Teitler M (1992) Molecular pharmacological differences in the interaction of serotonin with 5-hydroxytryptamine_{1C} and 5-hydroxytryptamine₂ receptors. *Mol Pharmacol.*, 42(2):328-35.

The functional properties of compounds (efficacy and potency) were determined in whole cells expressing 5-HT_{2A} or 5-HT_{2C} receptors by assessing their ability to stimulate or inhibit receptor-mediated phosphoinositol hydrolysis. The procedures used are described below.

IN VITRO BINDING ASSAYS

Stable expression of 5-HT_{2A} and 5-HT_{2C} receptors in HEK293E cells.

Stable cell lines were generated by transfecting 293EBNA cells with plasmids containing human 5-HT_{2A}, 5-HT_{2B}, or 5-HT_{2C} (VNV edited isoform) cDNA using calcium phosphate. These plasmids also contained the cytomegalovirus (CMV) immediate early promoter to drive receptor expression and EBV oriP for their maintenance as an extrachromosomal element, and the hph gene from *E. Coli* to yield hygromycin B resistance (Horlick et al., 1997). Transfected cells were maintained in Dulbecco's Modified Eagle medium (DMEM) containing dialyzed 10% fetal bovine serum at 37°C in a humid environment (5% CO₂) for 10 days. The 5-HT_{2A} cells were adapted to spinner culture for bulk processing whereas it was necessary to maintain the other lines as adherent cultures. On the day of harvest, cells were washed in phosphate-buffered saline (PBS), counted, and stored at -80 °C.

Membrane Preparation

On the day of assay, pellets of whole cells (containing approximately 1×10^8 cells) expressing the 5-HT_{2A} or 5-HT_{2C} receptor were thawed on ice and homogenized in 50 mM Tris HCl (pH 7.7) containing 1.0 mM EDTA using a Brinkman Polytron (PT-10, setting 6 for 10 sec). The homogenate was centrifuged at 48,000 x g for 10 min and the resulting pellet washed twice by repeated homogenization and centrifugation steps. The final pellet was resuspended in tissue buffer and protein determinations were made by the bichichoninic acid (BCA) assay (Pierce Co., IL) using bovine serum albumin as the standard.

Radioligand binding assays for the 5-HT_{2A} ,and 5-HT_{2C} receptors

Radioligand binding studies were conducted to determine the binding affinities (K_i values) of compounds for the human recombinant 5-HT_{2A}, 5-HT_{2B}, and 5-HT_{2C} receptors (Fitzgerald et al., 1999). Assays were conducted in disposable polypropylene 96-well plates (Costar Corp., Cambridge, MA) and were initiated by the addition of 5-HT_{2A} , 5-HT_{2B}, or 5-HT_{2C} membrane homogenate in tissue buffer (10-30 (g/well) to assay buffer (50 mM Tris HCl, 0.5 mM EDTA, 10 mM pargyline, 10 mM MgSO₄, 0.05 % ascorbic acid, pH 7.5) containing [¹²⁵I]DOI for the 5-HT_{2A} and 5-HT_{2C} receptors (0.3-0.5 nM, final) or [³H]LSD (2-2.5 nM, final) for the 5-HT_{2B} receptor, with or without competing drug (i.e, newly synthesized chemical entity). For a typical competition experiment, a fixed concentration of radioligand was competed with duplicate concentrations of ligand (12 concentrations ranging from 10 picomolar to 10 micromolar). The reaction mixtures were incubated to equilibrium for 45 min at 37°C and terminated by rapid filtration (cell harvester; Inotech Biosystems Inc., Lansing, MI) over GFF glass-fiber filters that had been pre-soaked in 0.3% polyethyleneimine. Filters were washed in ice-cold 50 mM Tris HCl buffer (pH 7.5) and then counted in a gamma counter for the 5-HT_{2A} and 5-HT_{2C} assays, or by liquid scintillation spectroscopy for the 5-HT_{2B} assay.

Phosphoinositide hydrolysis studies

The ability of newly synthesized compounds to stimulate phosphoinositide (PI) hydrolysis was monitored in whole cells using a variant (Egan et al., 1998) of a protocol described previously (Berridge et al., 1982). HEK293E cells expressing the human 5-HT_{2A}, 5-HT_{2B}, or 5-HT_{2C} receptor were lifted with 0.5 mM EDTA and plated at a density of 100,000/well onto poly-D-lysine-coated 24-well plates (Biocoat; Becton Dickinson, Bedford, MA) in Dulbecco's modified Eagle's serum (DMEM; Gibco BRL) containing high glucose, 2mM glutamine, 10% dialyzed fetal calf serum, 250 (g/ml hygromycin B, and 250(g/ml G418. Following a 24-48 hr period, the growth media was removed and replaced with DMEM without fetal calf serum and inositol (Gibco BRL). The cells were then incubated with DMEM (without serum and inositol) containing a final concentration of 0.5 uCi/well myo-[³H]inositol for 16-18 hr. Following this incubation, the cells were washed with DMEM (without serum or inositol) containing 10 mM LiCl and 10 (M pargyline and then incubated for 30 min with the same media but now containing one of several test compounds. Reactions were terminated by aspirating the media and lysing the cells by freeze-thaw. [³H]phosphoinositides were extracted with chloroform/methanol (1:2 v/v), separated by anion exchange chromatography (Bio-Rad AGI-X8 resin), and counted by liquid scintillation spectroscopy as described previously (Egan et al., 1998).

Data analyses

The equilibrium apparent dissociation constants (K_i's) from the competition experiments were calculated using an iterative nonlinear regression curve-fitting program (GraphPad Prism; San Diego, CA). For the PI hydrolysis experiments, EC₅₀'s were calculated using a one-site 'pseudo' Hill model: $y = ((R_{max} - R_{min}) / (1 + R / EC_{50}^{nH})) + R_{min}$ where R= response (DeltaGraph, Monterey, CA). E_{max} (maximal response) was derived from the fitted curve maxima (net IP stimulation) for each compound. Intrinsic activity (IA) was determined by expressing the E_{max} of a compound as a percentage of the E_{max} of 5-HT (IA=1.0).

IN VIVO EXPERIMENTS FOR SEROTONERGIC LIGANDS

Preclinical Efficacy, Potency, and Side Effect Liability

a) Anti-Serotonin Efficacy

Antagonism of Quipazine-Induced Head Twitch in Rat. Quipazine, an
5 agonist at 5-HT receptors, produces a characteristic head twitch response in rats. 5-HT receptor antagonists effectively antagonize this 5-HT agonist-induced behavioral effect (Lucki et al., 1984). Accordingly, the quipazine-induced head twitch model in rat can function as an in vivo behavioral correlate to 5-HT receptor binding. Compounds are administered 30 minutes before behavioral testing (and 25 minutes
10 before quipazine), and a dose-related antagonism of the quipazine response is determined.

b) Antipsychotic Efficacy

Inhibition of the Conditioned Avoidance Response (CAR) in Rat. Rats are
15 trained to consistently avoid (by climbing onto a pole suspended from the ceiling of the test chamber) an electric foot shock (0.75 mA) delivered to the grid floor of the testing chamber. All antipsychotic drugs effectively inhibit this conditioned avoidance response (Arnt, 1982). The ability of a compound to inhibit this response is used to determine the antipsychotic efficacy of potential drug candidates.

20

c) Extrapyramidal Side Effect Liability

Induction of Catalepsy in Rat. Typical antipsychotic drugs produce
extrapyramidal side effects (EPS) at clinically effective doses. The most widely
accepted preclinical indicator of EPS liability in humans is a drug-induced catalepsy
25 syndrome in rat (Costall and Naylor, 1975), a condition whereby the animal will remain immobile in an externally imposed posture (analogous to a catatonic stupor in humans). Rats are tested for induction of catalepsy in a dose-response test after oral administration of compounds.

30 d) CNS penetration; In vivo brain receptor occupancy

In Vivo Binding. To determine the level of in vivo receptor occupancy, an in vivo receptor binding protocol is used. This procedure uses an appropriate

radioligand to label the receptor of interest. For example, to measure both Dopamine D2 and 5-HT_{2A} receptors in vivo, one can use ³H-N-methyl spiperone (³H -NMSP), (Frost, et. al. 1987) The procedure uses rats (or mice) fasted overnight. To measure the effects of compounds on the receptors of interest, compounds are dosed, usually p.o. for example in 2 microliters/gram body weight in 0.25% Methocel suspension. The radiolabeled compound (in this example, ³H-NMSP) is administered by i.v. tail vein injection (10 microcuries label/200 gram rat). Time course experiments are used to determine the optimal time of binding for both the radiolabeled and unlabeled compound. These optimal time frames are used for all subsequent dose-response experiments. After the appropriate time frame of compound/radioligand exposure, the animals are sacrificed and the relevant brain regions dissected (frontal cortex for 5-HT_{2A} and striatum for D2 receptors) and examined for their content of radioactivity. The level of non-specific binding is determined by examining a brain region known not to contain the receptor of interest (in this case the cerebellum) or by administering an excess of compound known pharmacologically to interact with the receptor.

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DOSAGE AND FORMULATION

- The serotonin agonist and serotonin antagonist compounds of this invention
20 can be administered as treatment for the control or prevention of central nervous system disorders including obesity, anxiety, depression, psychosis, schizophrenia, sleep and sexual disorders, migraine and other conditions associated with cephalic pain, social phobias, and gastrointestinal disorders such as dysfunction of the gastrointestinal tract motility by any means that produces contact of the active agent
25 with the agent's site of action, i.e., 5-HT₂ receptors, in the body of a mammal. It can be administered by any conventional means available for use in conjunction with pharmaceuticals, either as an individual therapeutic agent or in a combination of therapeutic agents. It can be administered alone; but preferably is administered with a pharmaceutical carrier selected on the basis of the chosen route of administration and
30 standard pharmaceutical practice.

The compounds of the present invention can be administered in such oral dosage forms as tablets, capsules (each of which includes sustained release or timed

release formulations), pills, powders, granules, elixirs, tinctures, suspensions, syrups, and emulsions. Likewise, they may also be administered in intravenous (bolus or infusion), intraperitoneal, subcutaneous, or intramuscular form, all using dosage forms well known to those of ordinary skill in the pharmaceutical arts.

5 The dosage administered will, of course, vary depending upon known factors, such as the pharmacodynamic characteristics of the particular agent and its mode and route of administration; the age, health and weight of the recipient; the nature and extent of the symptoms; the kind of concurrent treatment; the frequency of treatment; and the effect desired. By way of general guidance, a daily dosage of active
10 ingredient can be expected to be about 0.001 to about 1000 milligrams per kilogram of body weight, with the preferred dose being about 0.01 to about 100 mg/kg; with the more preferred dose being about 0.1 to about 30 mg/kg. Advantageously, compounds of the present invention may be administered in a single daily dose, or the total daily dosage may be administered in divided doses of two, three, or four times daily.

15 Dosage forms of compositions suitable for administration contain from about 1 mg to about 100 mg of active ingredient per unit. In these pharmaceutical compositions the active ingredient will ordinarily be present in an amount of about 0.5-95% by weight based on the total weight of the composition. The active
20 ingredient can be administered orally in solid dosage forms, such as capsules, tablets and powders, or in liquid dosage forms, such as elixirs, syrups and suspensions. It can also be administered parenterally, in sterile liquid dosage forms.

 Gelatin capsules contain the active ingredient and powdered carriers, such as lactose, starch, cellulose derivatives, magnesium stearate, stearic acid, and the like. Similar diluents can be used to make compressed tablets. Both tablets and capsules
25 can be manufactured as sustained release products to provide for continuous release of medication over a period of hours. Compressed tablets can be sugar coated or film coated to mask any unpleasant taste and protect the tablet from the atmosphere, or enteric coated for selective disintegration in the gastrointestinal tract. Liquid dosage forms for oral administration can contain coloring and flavoring to increase patient
30 acceptance.

 In general, water, a suitable oil, saline, aqueous dextrose (glucose), and related sugar solutions and glycols such as propylene glycol or polyethylene glycols are

suitable carriers for parenteral solutions. Solutions for parenteral administration preferably contain a water soluble salt of the active ingredient, suitable stabilizing agents, and if necessary, buffer substances. Antioxidizing agents such as sodium bisulfite, sodium sulfite, or ascorbic acid, either alone or combined, are suitable stabilizing agents. Also used are citric acid and its salts, and sodium EDTA. In addition, parenteral solutions can contain preservatives, such as benzalkonium chloride, methyl- or propyl-paraben and chlorobutanol. Suitable pharmaceutical carriers are described in *Remington's Pharmaceutical Sciences, supra*, a standard reference text in this field.

Useful pharmaceutical dosage-forms for administration of the compounds of this invention can be illustrated as follows:

Capsules

A large number of unit capsules can be prepared by filling standard two-piece hard gelatin capsules each with 100 mg of powdered active ingredient, 150 mg of lactose, 50 mg of cellulose, and 6 mg magnesium stearic.

Soft Gelatin Capsules

A mixture of active ingredient in a digestible oil such as soybean oil, cottonseed oil or olive oil can be prepared and injected by means of a positive displacement pump into gelatin to form soft gelatin capsules containing 100 mg of the active ingredient. The capsules should then be washed and dried.

Tablets

A large number of tablets can be prepared by conventional procedures so that the dosage unit is 100 mg of active ingredient, 0.2 mg of colloidal silicon dioxide, 5 milligrams of magnesium stearate, 275 mg of microcrystalline cellulose, 11 mg of starch and 98.8 mg of lactose. Appropriate coatings may be applied to increase palatability or delay absorption.

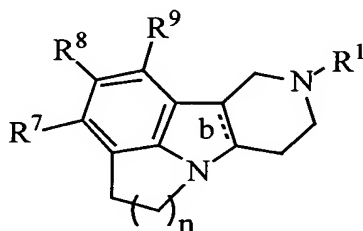
Suspension

An aqueous suspension can be prepared for oral administration so that each 5 ml contain 25 mg of finely divided active ingredient, 200 mg of sodium carboxymethyl cellulose, 5 mg of sodium benzoate, 1.0 g of sorbitol solution, U.S.P., and 0.025 mg of vanillin.

Injectable

A parenteral composition suitable for administration by injection can be prepared by stirring 1.5% by weight of active ingredient in 10% by volume propylene glycol and water. The solution is sterilized by commonly used techniques.

The Tables below provide representative Examples, the synthesis of which are described above, of the compounds of Formula (I) of the present invention.

TABLE 1

Ex#	n	R7	R8	R9	b	R1
1	1	H	H	H	dbl	H
2	1	H	H	H	dbl	cycPropyl
3	1	H	H	H	sgl	H
16	2	H	H	H	dbl	H
17	2	H	H	H	sgl	H
37	1	H	H	H	sgl	-C(=O)cycPropyl
38	1	H	H	H	sgl	-C(=O)iPropyl
89	1	H	2-Cl-phenyl	H	sgl	-CO ₂ -tButyl
90	1	H	2,4-diCl-phenyl	H	sgl	-CO ₂ -tButyl
91	1	H	3,4-diCl-phenyl	H	sgl	-CO ₂ -tButyl
92	1	H	2,3-diCl-phenyl	H	sgl	-CO ₂ -tButyl
93	1	H	2-Cl-4-CF ₃ -phenyl	H	sgl	-CO ₂ -tButyl

Ex#	n	R7	R8	R9	b	R1
94	1	H	2-Cl-4-MeO-phenyl	H	sgl	-CO ₂ -tButyl
95	1	H	2-MeO-4-iPr-phenyl	H	sgl	-CO ₂ -tButyl
96	1	H	3-F-phenyl	H	sgl	-CO ₂ -tButyl
97	1	H	2,4-diMeO-phenyl	H	sgl	-CO ₂ -tButyl
98	1	H	2-Cl-phenyl	H	sgl	H
99	1	H	2,4-diCl-phenyl	H	sgl	H
100	1	H	3,4-diCl-phenyl	H	sgl	H
101	1	H	2,3-diCl-phenyl	H	sgl	H
102	1	H	2-Cl-4-CF ₃ -phenyl	H	sgl	H
103	1	H	2-Cl-4-MeO-phenyl	H	sgl	H
104	1	H	2-MeO-4-iPr-phenyl	H	sgl	H
105	1	H	3-F-phenyl	H	sgl	H
106	1	H	2,4-diMeO-phenyl	H	sgl	H
107	2	H	H	H	sgl	-CO ₂ -tButyl
108	2	H	Br	H	sgl	-CO ₂ -tButyl
109	2	H	2,3-diCl-phenyl	H	sgl	-CO ₂ -tButyl
110	2	H	3,4-diCl-phenyl	H	sgl	-CO ₂ -tButyl
111	2	H	2-Cl-4-CF ₃ -phenyl	H	sgl	-CO ₂ -tButyl
112	2	H	2,3-diCl-phenyl	H	sgl	H
113	2	H	3,4-diCl-phenyl	H	sgl	H
114	2	H	2-Cl-4-CF ₃ -phenyl	H	sgl	H
189	1	H	2-Cl-phenyl	H	sgl	-(CH ₂) ₃ C(=O)(4-F-phenyl)
190	1	H	2,4-diCl-phenyl	H	sgl	-(CH ₂) ₃ C(=O)(4-F-phenyl)
191	2	H	H	H	sgl	-(CH ₂) ₃ C(=O)(4-F-phenyl)
265	1	H	H	H	sgl	-(CH ₂) ₃ C(=O)(4-F-phenyl)
274	1	H	2-F-4-MeO-phenyl	H	sgl	H
275	1	H	2-CF ₃ -4-EtO-phenyl	H	sgl	-CO ₂ -tButyl
276	1	H	2-CF ₃ -4-EtO-phenyl	H	sgl	H
277	1	H	2-F-4-Cl-phenyl	H	sgl	-CO ₂ -tButyl
278	1	H	2-F-4-Cl-phenyl	H	sgl	H
279	1	H	2-CF ₃ -4-iPrO-phenyl	H	sgl	-CO ₂ -tButyl
280	1	H	2-CF ₃ -4-iPrO-phenyl	H	sgl	H
281	1	H	2-CF ₃ -4-MeO-phenyl	H	sgl	-CO ₂ -tButyl
282	1	H	2-CF ₃ -4-MeO-phenyl	H	sgl	H
283	1	H	phenyl	H	sgl	-CO ₂ -tButyl
284	1	H	phenyl	H	sgl	H
285	1	H	2-Me-phenyl	H	sgl	-CO ₂ -tButyl
286	1	H	2-Me-phenyl	H	sgl	H
287	1	H	2-CF ₃ -phenyl	H	sgl	-CO ₂ -tButyl
288	1	H	2-CF ₃ -phenyl	H	sgl	H
289	1	H	3,4-diMeO-phenyl	H	sgl	-CO ₂ -tButyl
290	1	H	3,4-diMeO-phenyl	H	sgl	H
291	1	H	2,4-diCl-phenyl	H	sgl	-CO ₂ -tButyl
292	1	H	2,4-diCl-phenyl	H	sgl	H
293	1	H	3,5-diCl-phenyl	H	sgl	-CO ₂ -tButyl
294	1	H	3,5-diCl-phenyl	H	sgl	H

Ex#	n	R7	R8	R9	b	R1
295	1	H	4-MeO-2-iPr-phenyl	H	sgl	-CO ₂ -tButyl
296	1	H	4-MeO-2-iPr-phenyl	H	sgl	H
297	1	H	5-F-4-MeO-2-Me-phenyl	H	sgl	-CO ₂ -tButyl
298	1	H	5-F-4-MeO-2-Me-phenyl	H	sgl	H
299	1	H	4-MeO-2-Me-phenyl	H	sgl	-CO ₂ -tButyl
300	1	H	4-MeO-2-Me-phenyl	H	sgl	H
301	1	H	2-Cl-4-MeO-phenyl	H	sgl	-CO ₂ -tButyl
302	1	H	2-Cl-4-MeO-phenyl	H	sgl	H
303	1	H	4-Cl-2-Me-phenyl	H	sgl	-CO ₂ -tButyl
304	1	H	4-Cl-2-Me-phenyl	H	sgl	H
305	1	H	2-CHO-4-MeO-phenyl	H	sgl	H
306	1	H	2,6-diCl-phenyl	H	sgl	H
307	1	H	2-CF ₃ -4-MeNH-phenyl	H	sgl	H
308	1	H	2-CF ₃ -4-NH ₂ -phenyl	H	sgl	H
309	1	H	4-MeO-2-CH ₃ CH(OH)-phenyl	H	sgl	H
310	3	H	H	H	sgl	H
311	3	H	H	H	sgl	-CO ₂ -tButyl
312	3	H	H	H	sgl	H
313	3	H	H	H	sgl	H
314	3	H	H	H	sgl	-CO ₂ -tButyl
315	3	H	2,4-diCl-phenyl	H	sgl	H
316	3	H	2,3-diCl-phenyl	H	sgl	H
317	3	H	3,4-diCl-phenyl	H	sgl	H
318	3	H	3,5-diCl-phenyl	H	sgl	H
319	3	H	2,5-diCl-phenyl	H	sgl	H
320	3	H	2,6-diCl-phenyl	H	sgl	H
321	3	H	2-Cl-phenyl	H	sgl	H
322	3	H	3-Cl-phenyl	H	sgl	H
323	3	H	4-Cl-phenyl	H	sgl	H
324	3	H	2,6-diF-phenyl	H	sgl	H
325	3	H	2,6-diF-phenyl	H	sgl	H
326	3	H	2,3-diF-phenyl	H	sgl	H
327	3	H	3,4-diF-phenyl	H	sgl	H
328	3	H	3-F-phenyl	H	sgl	H
329	3	H	2-Cl-4-CF ₃ -phenyl	H	sgl	H
330	3	H	2-Cl-4-MeO-phenyl	H	sgl	H
331	3	H	2-F-4-MeO-phenyl	H	sgl	H
332	3	H	4-MeO-2-Me-phenyl	H	sgl	H
333	3	H	2-CF ₃ -4-MeO-phenyl	H	sgl	H
334	3	H	2-CF ₃ -phenyl	H	sgl	H
335	3	H	2-CF ₃ -4-iPrO-phenyl	H	sgl	H
336	3	H	2,4-diCF ₃ -phenyl	H	sgl	H
337	3	H	2-F-2-CF ₃ -phenyl	H	sgl	H
338	3	H	2-CF ₃ -4-NH ₂ -phenyl	H	sgl	H
339	3	H	2-CF ₃ -4-MeNH-phenyl	H	sgl	H
340	3	H	2-CHO-phenyl	H	sgl	H
341	3	H	2-CH ₂ (OH)-phenyl	H	sgl	H
342	3	H	4-MeO-2-CHO-phenyl	H	sgl	H
343	3	H	4-MeO-2-CH ₂ (OH)-phenyl	H	sgl	H

Ex#	n	R7	R8	R9	b	R1
344	3	H	4-CN-2-Me-phenyl	H	sgl	H
345	3	H	4-MeO-2-CH ₃ CH(OH)-phenyl	H	sgl	H
346	2	H	Br	H	sgl	-CO ₂ -tButyl
347	2	H	2,4-diCl-phenyl	H	sgl	H
348	2	H	3,4-diCl-phenyl	H	sgl	H
349	2	H	3,5-diCl-phenyl	H	sgl	H
350	2	H	2,5-diCl-phenyl	H	sgl	H
351	2	H	2,6-diCl-phenyl	H	sgl	H
352	2	H	2-Cl-phenyl	H	sgl	H
353	2	H	3-Cl-phenyl	H	sgl	H
354	2	H	4-Cl-phenyl	H	sgl	H
355	2	H	2,6-diF-phenyl	H	sgl	H
356	2	H	2,6-diF-phenyl	H	sgl	Me
357	2	H	2,3-diF-phenyl	H	sgl	H
358	2	H	3,4-diF-phenyl	H	sgl	H
359	2	H	3-F-phenyl	H	sgl	H
360	2	H	2-Cl-4-MeO-phenyl	H	sgl	H
361	2	H	2-F-4-MeO-phenyl	H	sgl	H
362	2	H	4-MeO-2-Me-phenyl	H	sgl	H
363	2	H	2-CF ₃ -4-MeO-phenyl	H	sgl	H
364	2	H	2-CF ₃ -4-MeO-phenyl	H	dbl	H
365	2	H	2-CF ₃ -4-OH-phenyl	H	sgl	H
366	2	H	2-CF ₃ -phenyl	H	sgl	H
367	2	H	2-CF ₃ -4-iPrO-phenyl	H	sgl	H
368	2	H	2,4-diCF ₃ -phenyl	H	sgl	H
369	2	H	2-CF ₃ -4-F-phenyl	H	sgl	H
370	2	H	2-CF ₃ -4-NH ₂ -phenyl	H	sgl	H
371	2	H	2-CF ₃ -4-MeNH-phenyl	H	sgl	H
372	2	H	4-CN-2-Me-phenyl	H	sgl	H
373	2	H	2-CHO-phenyl	H	sgl	H
374	2	H	2-CH ₂ (OH)-phenyl	H	sgl	H
375	2	H	4-MeO-2-CHO-phenyl	H	sgl	H
376	2	H	4-MeO-2-CH ₃ CH(OH)-phenyl	H	sgl	H
377	3	H	2-CF ₃ -4-EtO-phenyl	H	sgl	H
378	2	H	2-CF ₃ -4-EtO-phenyl	H	sgl	H
379	3	H	3-Cl-2-Me-phenyl	H	sgl	H
380	2	H	3-Cl-2-Me-phenyl	H	sgl	H
381	2	H	5-F-2-Me-phenyl	H	sgl	H
382	2	H	2,3-diCl-phenyl	H	sgl	Pr
383	2	H	2,3-diCl-phenyl	H	sgl	Pr
384	2	H	2,3-diCl-phenyl	H	sgl	Bu
385	2	H	2,3-diCl-phenyl	H	sgl	Bu
386	2	H	2,3-diCl-phenyl	H	sgl	4-pentenyl
387	2	H	2,3-diCl-phenyl	H	sgl	3-Me-2-butenyl
388	2	H	2,4-diCl-phenyl	H	sgl	Pr
389	2	H	2,4-diCl-phenyl	H	sgl	Bu
390	2	H	2,4-diCl-phenyl	H	sgl	4-pentenyl
391	2	H	2,4-diCl-phenyl	H	sgl	3-Me-2-butenyl
392	2	H	2,4-diCl-phenyl	H	sgl	cyclobutylmethyl
393	2	H	2-CF ₃ -4-MeO-phenyl	H	sgl	Me

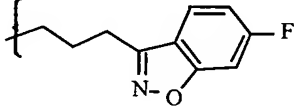
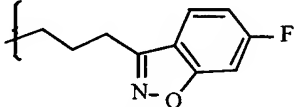
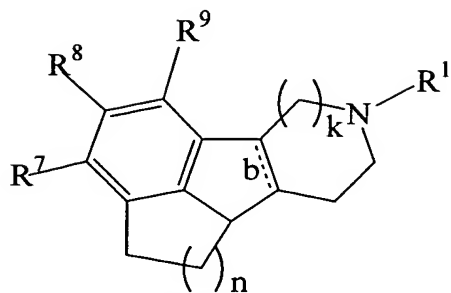
Ex#	n	R7	R8	R9	b	R1
394	2	H	2-CF ₃ -4-MeO-phenyl	H	sgl	Et
395	2	H	2-CF ₃ -4-MeO-phenyl	H	sgl	Pr
396	2	H	2-CF ₃ -4-MeO-phenyl	H	sgl	Bu
397	2	H	2-CF ₃ -4-MeO-phenyl	H	sgl	4-pentenyl
398	2	H	2-CF ₃ -4-MeO-phenyl	H	sgl	3-Me-2-butenyl
399	2	H	2-CF ₃ -4-MeO-phenyl	H	sgl	2-F-ethyl
400	2	H	2-CF ₃ -4-MeO-phenyl	H	sgl	2,2-diF-ethyl
401	2	H	2-CF ₃ -4-MeO-phenyl	H	sgl	cyclobutylmethyl
402	2	H	H	H	sgl	-(CH ₂) ₃ C(=O)(4-F-phenyl)
403	2	H	H	H	sgl	-(CH ₂) ₃ C(=O)(4-F-phenyl)
403	2	H	H	H	sgl	-(CH ₂) ₃ C(=O)(4-F-phenyl)
404	2	H	H	H	sgl	-(CH ₂) ₃ C(=O)(2-NH ₂ -phenyl)
405	2	H	H	H	sgl	-(CH ₂) ₃ C(=O)(2-NH ₂ -phenyl)
406	2	H	H	H	sgl	-(CH ₂) ₃ O(4-F-phenyl)
407	2	H	H	H	sgl	-(CH ₂) ₃ C(=O)(4-pyridyl)
408	2	H	H	H	sgl	
409	2	H	H	H	sgl	
410	2	H	H	H	dbl	-(CH ₂) ₃ C(=O)(4-F-phenyl)
411	3	H	H	H	sgl	-(CH ₂) ₃ C(=O)(4-F-phenyl)
412	3	H	H	H	sgl	-(CH ₂) ₃ C(=O)(4-F-phenyl)
413	3	H	H	H	sgl	-(CH ₂) ₃ C(=O)(4-F-phenyl)
414	3	H	H	H	sgl	-(CH ₂) ₃ C(=O)(4-F-2-NH ₂ -phenyl)
415	2	H	H	H	sgl	-(CH ₂) ₃ C(=O)(4-F-2-NH ₂ -phenyl)
416	2	H	H	H	sgl	-(CH ₂) ₃ C(=O)(4-F-2-NH ₂ -phenyl)
417	2	H	H	H	sgl	-(CH ₂) ₃ C(=O)(4-F-2-NH ₂ -phenyl)

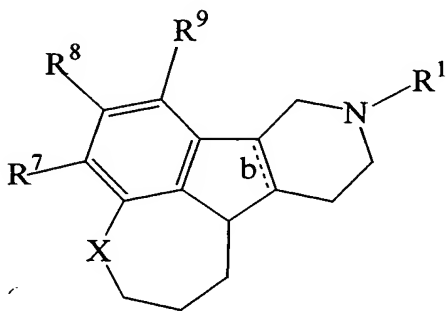
TABLE 2



Ex#	n	k	R7	R8	R9	b	R1
418	2	2	H	H	H	dbl	H
419	2	2	H	H	H	sgl	H
420	2	2	H	H	H	sgl	-(CH ₂) ₃ C(=O)(4-F-phenyl)
421	2	2	H	H	H	sgl	-(CH ₂) ₃ C(=O)(4-F-2-NH ₂ -phenyl)
422	3	2	H	H	H	dbl	H
423	3	2	H	H	H	sgl	H
424	3	2	H	H	H	sgl	-(CH ₂) ₃ C(=O)(4-F-phenyl)
425	3	2	H	H	H	sgl	-(CH ₂) ₃ C(=O)(4-F-2-NH ₂ -phenyl)
434	2	1	H	H	H	sgl	H
435	2	1	H	H	H	sgl	-CO ₂ -tButyl
436	2	1	H	Br	H	sgl	-CO ₂ -tButyl
437	2	1	H	2-CF ₃ -4-MeO-phenyl	H	sgl	H

5

TABLE 3

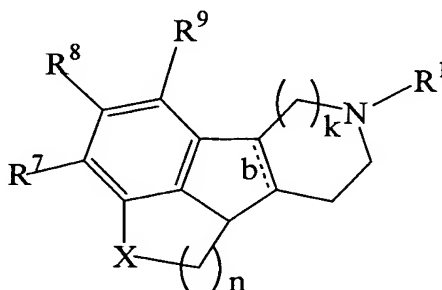


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Ex#	X	R7	R8	R9	b	R1
426	C=O	H	H	H	sgl	H
427	C=O	H	H	H	sgl	-CO ₂ -tButyl
428	C=O	H	2,4-diCl-phenyl	H	sgl	-CO ₂ -tButyl

Ex#	X	R7	R8	R9	b	R1
429	C=O	H	2,4-diCl-phenyl	H	sg1	H
430	C=O	H	2,4-diCl-phenyl	H	sg1	H
431	C=O	H	2,4-diCl-phenyl	H	sg1	H
432	CH(OH)	H	2,4-diCl-phenyl	H	sg1	H
433	CH(OH)	H	2,4-diCl-phenyl	H	sg1	H

TABLE 4

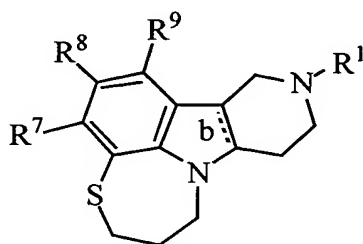


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Ex#	X	n	k	R7	R8	R9	b	R1
196	NHCO	1	1	H	H	H	db1	-(CH ₂) ₃ C(=O)(4-F-phenyl)
210	NMe	2	1	H	H	H	sg1	-(CH ₂) ₃ C(=O)(4-pyridyl)
211	NH	2	1	H	H	H	sg1	H
212	NH	2	1	H	H	H	sg1	-(CH ₂) ₃ C(=O)(4-F-phenyl)
217	NMe	2	1	H	H	H	sg1	
218	NMe	2	1	H	H	H	sg1	
255	NMe	2	1	H	H	H	sg1	H
256	NEt	2	1	H	H	H	sg1	H
257	NPr	2	1	H	H	H	sg1	H
258	N(i-Pr)	2	1	H	H	H	sg1	H
259	N(n-Bu)	2	1	H	H	H	sg1	H
260	N(CH ₂ Ph)	2	1	H	H	H	sg1	H
261	NMe	2	1	H	H	H	sg1	-(CH ₂) ₃ C(=O)(4-F-phenyl)
262	NEt	2	1	H	H	H	sg1	-(CH ₂) ₃ C(=O)(4-F-phenyl)
263	N(i-Pr)	2	1	H	H	H	sg1	-(CH ₂) ₃ C(=O)(4-F-phenyl)
264	N(CH ₂ Ph)	2	1	H	H	H	sg1	-(CH ₂) ₃ C(=O)(4-F-phenyl)
269	NMe	2	1	H	H	H	sg1	-(CH ₂) ₃ O(4-F-phenyl)
N274	NMe	2	1	H	2,4-diCl-phenyl	H	sg1	H
N275	NH	2	1	H	2,4-diCl-phenyl	H	sg1	H
N276	NMe	2	1	H	Br	H	sg1	-(CH ₂) ₃ C(=O)(4-F-phenyl)
N277	NMe	2	1	H	MeO	H	sg1	-(CH ₂) ₃ C(=O)(4-F-phenyl)

Ex#	X	n	k	R7	R8	R9	b	R1
N278	NMe	2	1	H	2,4-diCl-phenyl	H	sgl	H
N279	NH	3	1	H	4-MeO-2-Me-phenyl	H	sgl	H
N280	NHCO	2	1	H	2,4-diCl-phenyl	H	sgl	H
N281	NMe	2	2	H	H	H	sgl	H
N282	NMe	2	2	H	H	H	sgl	-(CH ₂) ₃ C(=O)(4-F-phenyl)
N283	NHCH(Me)	1	1	H	2,4-diCl-phenyl	H	sgl	H

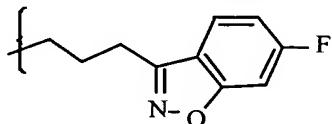
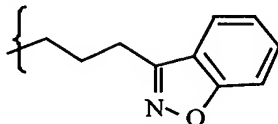
TABLE 5

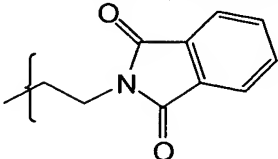
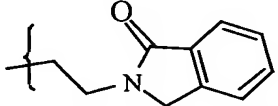


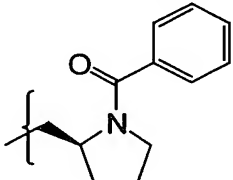
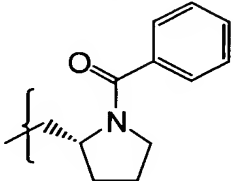
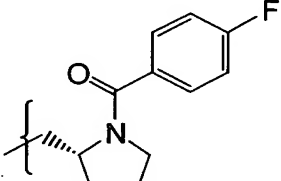
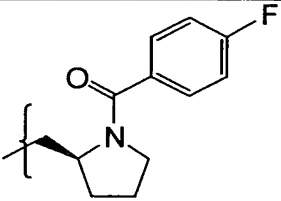
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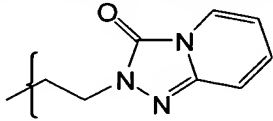
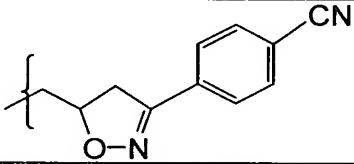
Ex#	R7	R8	R9	b	R1
4	H	H	F	dbl	-CO ₂ Et
5	H	H	F	dbl	H
6	H	H	Me	dbl	H
7	H	H	Me	dbl	-CO ₂ -tBu
8	H	H	Me	sgl	H
9	H	H	H	sgl	H
10	H	H	NO ₂	dbl	H
11	H	H	NO ₂	sgl	H
12	Cl	H	H	dbl	H
13	Cl	H	H	sgl	H
14	Me	H	H	dbl	H
15	Me	H	H	sgl	H
18	H	H	Br	dbl	H
19	H	H	Br	sgl	H
25	H	H	H	sgl	-C(=O)(3,4-diMeO-phenyl)
26	H	H	H	sgl	-C(=O)(2,5-diMeO-phenyl)
27	H	H	H	sgl	-C(=O)(3,5-diMeO-phenyl)
28	H	H	H	sgl	2,6-diMeO-benzyl
29	H	H	H	sgl	2,4-diMeO-benzyl
30	H	H	H	sgl	2,4,6-triMeO-benzyl
31	H	H	H	sgl	2,3-diMeO-benzyl
32	H	H	H	sgl	2,4,5-triMeO-benzyl
33	H	H	H	sgl	cyclohexylmethyl
34	H	H	H	sgl	2,3,4-triMeO-benzyl
35	H	H	H	sgl	3,4-diMeO-benzyl
36	H	H	H	sgl	3,4,5-triMeO-benzyl
39	H	H	H	sgl	-CO ₂ Et
40	H	-C(=O)CH ₃	H	sgl	-CO ₂ Et

Ex#	R7	R8	R9	b	R1
41	H	-NHC(=O)CH ₃	H	sgl	-CO ₂ Et
42	H	H	H	sgl	-CH ₂ CH ₂ (4-F-phenyl)
43	H	H	H	sgl	Et
44	H	H	H	sgl	Pr
45	H	H	H	sgl	butyl
46	H	H	H	sgl	pentyl
47	H	H	H	sgl	hexyl
48	H	H	H	sgl	2-propyl
49	H	H	H	sgl	2-butyl
50	H	H	H	sgl	2-pentyl
51	H	H	H	sgl	2-hexyl
52	H	H	H	sgl	2-Me-propyl
53	H	H	H	sgl	2-Me-butyl
54	H	H	H	sgl	2-Me-pentyl
55	H	H	H	sgl	2-Et-butyl
56	H	H	H	sgl	3-Me-pentyl
57	H	H	H	sgl	3-Me-butyl
58	H	H	H	sgl	4-Me-pentyl
59	H	H	H	sgl	cyclopropylmethyl
60	H	H	H	sgl	cyclobutylmethyl
61	H	H	H	sgl	cyclohexylmethyl
62	H	H	H	sgl	2-propenyl
63	H	H	H	sgl	2-Me-2-propenyl
64	H	H	H	sgl	trans-2-butenyl
65	H	H	H	sgl	3-Me-butenyl
66	H	H	H	sgl	3-butenyl
67	H	H	H	sgl	trans-2-pentenyl
68	H	H	H	sgl	cis-2-pentenyl
69	H	H	H	sgl	4-pentenyl
70	H	H	H	sgl	4-Me-3-pentenyl
71	H	H	H	sgl	3,3-diCl-2-propenyl
72	H	H	H	sgl	benzyl
73	H	H	H	sgl	2-Me-benzyl
74	H	H	H	sgl	3-Me-benzyl
75	H	H	H	sgl	4-Me-benzyl
76	H	H	H	sgl	2,5-diMe-benzyl
77	H	H	H	sgl	2,4-diMe-benzyl
78	H	H	H	sgl	3,5-diMe-benzyl
79	H	H	H	sgl	2,4,6-triMe-benzyl
80	H	H	H	sgl	3-MeO-benzyl
81	H	H	H	sgl	3,5-diMeO-benzyl
82	H	H	H	sgl	pentafluorobenzyl
83	H	H	H	sgl	2-phenylethyl
84	H	H	H	sgl	1-phenyl-2-propyl
85	H	H	H	sgl	trans-3-phenyl-2-propenyl
86	H	H	H	sgl	4-phenylbutyl
87	H	H	H	sgl	4-phenylbenzyl
88	H	H	H	sgl	2-phenylbenzyl
169	H	Me	H	sgl	H
170	H	CN	H	sgl	H
171	H	Et	H	sgl	H
175	H	H	H	dbl	Me
176	H	H	H	sgl	Me

Ex#	R7	R8	R9	b	R1
177	H	H	H	sgl	H
178	Cl	H	H	sgl	-(CH ₂) ₃ C(=O)(4-F-phenyl)
179	Me	H	H	sgl	-(CH ₂) ₃ C(=O)(4-F-phenyl)
180	H	H	H	sgl	-(CH ₂) ₃ S(3-F-phenyl)
181	H	H	H	sgl	-(CH ₂) ₃ CH(OH)(4-F-phenyl)
186	H	H	H	sgl	-(CH ₂) ₃ C(=O)(4-F-phenyl)
187	H	MeO	H	sgl	-(CH ₂) ₃ C(=O)(4-F-phenyl)
192	H	H	H	sgl	-(CH ₂) ₃ C(=O)(4-Br-phenyl)
193	H	H	H	sgl	-(CH ₂) ₃ SO ₂ (3-F-phenyl)
194	H	H	H	sgl	-(CH ₂) ₃ C(=O)(4-(3,4-diCl-phenyl)phenyl)
197	H	H	H	sgl	-(CH ₂) ₃ C(=O)(4-Me-phenyl)
198	H	H	H	sgl	-(CH ₂) ₃ C(=O)(4-F-phenyl)
199	H	H	H	sgl	-(CH ₂) ₃ C(=O)(4-MeO-phenyl)
200	H	H	H	sgl	-(CH ₂) ₂ C(=O)(4-F-phenyl)
201	H	H	H	sgl	-(CH ₂) ₃ SO ₂ (4-F-phenyl)
202	H	H	H	sgl	-(CH ₂) ₃ S(=O)(4-F-phenyl)
203	H	H	H	sgl	-(CH ₂) ₃ O(4-F-phenyl)
204	H	H	H	sgl	-(CH ₂) ₃ O(phenyl)
205	H	H	H	sgl	-(CH ₂) ₃ S(4-F-phenyl)
206	H	H	H	sgl	-(CH ₂) ₃ NH(4-F-phenyl)
207	H	H	H	sgl	-(CH ₂) ₃ N(CH ₃)(4-F-phenyl)
208	H	H	H	sgl	-(CH ₂) ₃ C(=O)(4-pyridyl)
209	H	H	H	sgl	-(CH ₂) ₃ C(=O)(3-pyridyl)
214	H	H	H	sgl	
215	H	H	H	sgl	
219	H	H	H	sgl	-(CH ₂) ₃ CO ₂ Et
220	H	H	H	sgl	-(CH ₂) ₄ CO ₂ Et
221	H	H	H	sgl	-(CH ₂) ₃ C(=O)N(CH ₃)(OCH ₃)
222	H	H	H	sgl	-(CH ₂) ₄ C(=O)N(CH ₃)(OCH ₃)
223	H	H	H	sgl	-(CH ₂) ₃ C(=O)(3-Me-4-F-phenyl)
224	H	H	H	sgl	-(CH ₂) ₃ C(=O)(phenyl)
225	H	H	H	sgl	-(CH ₂) ₃ C(=O)(4-Cl-phenyl)
226	H	H	H	sgl	-(CH ₂) ₃ C(=O)(3-Me-phenyl)
227	H	H	H	sgl	-(CH ₂) ₃ C(=O)(4-tBu-phenyl)
228	H	H	H	sgl	-(CH ₂) ₃ C(=O)(3,4-diF-phenyl)
229	H	H	H	sgl	-(CH ₂) ₃ C(=O)(2-MeO-5-F-phenyl)
230	H	H	H	sgl	-(CH ₂) ₄ C(=O)(phenyl)

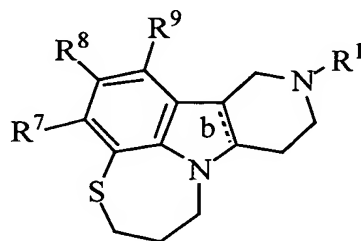
Ex#	R7	R8	R9	b	R1
231	H	H	H	sgl	$-(CH_2)_3C(=O)(4-F-1-naphthyl)$
232	H	H	H	sgl	$-(CH_2)_3C(=O)(benzyl)$
233	H	H	H	sgl	$-(CH_2)_2C(=O)NH(4-F-phenyl)$
234	H	H	H	sgl	$-(CH_2)_3C(=O)NH(4-F-phenyl)$
235	H	H	H	sgl	$-(CH_2)_3CH(OH)(4-F-phenyl)$
236	H	H	H	sgl	$-(CH_2)_3CH(OH)(4-pyridyl)$
237	H	H	H	sgl	$-(CH_2)_3CH(OH)(2,3-diMeO-phenyl)$
238	H	H	H	sgl	$-(CH_2)_3C(=O)(2,3-diMeO-phenyl)$
239	H	H	H	sgl	$-(CH_2)_4(cyclohexyl)$
240	H	H	H	sgl	$-(CH_2)_3CH(phenyl)_2$
241	H	H	H	sgl	$-CH_2CH_2CH=C(phenyl)_2$
242	H	H	H	sgl	$-(CH_2)_3CH(4-F-phenyl)_2$
243	H	H	H	sgl	$-CH_2CH_2CH=C(4-F-phenyl)_2$
244	H	H	H	sgl	$-(CH_2)_2NHC(=O)(phenyl)$
245	H	H	H	sgl	$-(CH_2)_2NHC(=O)(2-F-phenyl)$
246	H	H	H	sgl	$-(CH_2)_2NHC(=O)(4-F-phenyl)$
247	H	H	H	sgl	$-(CH_2)_3(3-indolyl)$
248	H	H	H	sgl	$-(CH_2)_3(1-Me-3-indolyl)$
249	H	H	H	sgl	$-CH_2CH_2(3-indolyl)$
250	H	H	H	sgl	$-(CH_2)_3(1-indolyl)$
251	H	H	H	sgl	$-(CH_2)_3(1-indolyl)$
252	H	H	H	sgl	$-(CH_2)_3(1-benzimidazolyl)$
253	H	H	H	sgl	
254	H	H	H	sgl	
268	H	F	H	sgl	$-(CH_2)_3C(=O)(4-F-phenyl)$
271	H	H	H	sgl	H
273	H	F	H	sgl	H
S274	Br	H	H	sgl	H
S275	2,6-diF-phenyl	H	H	sgl	H
S276	2-Me-4-MeO-phenyl	H	H	sgl	H
S277	4-CF ₃ -phenyl	H	H	sgl	H
S278	2,3-diCl-phenyl	H	H	sgl	H
S279	2,4-diCl-phenyl	H	H	sgl	H
S280	2-Cl-4-CF ₃ -phenyl	H	H	sgl	H
S281	CN	H	H	sgl	H
S282	CN	Br	H	sgl	H
S283	benzyl	H	H	sgl	H
S284	CHO	H	H	sgl	H
S285	CO ₂ H	H	H	sgl	H

Ex#	R7	R8	R9	b	R1
S286	H	H	H	sgl	$-(\text{CH}_2)_2\text{NHC}(=\text{O})(2,4\text{-diF-phenyl})$
S287	H	H	H	sgl	$-(\text{CH}_2)_2\text{NMeC}(=\text{O})\text{-phenyl}$
S288	H	H	H	sgl	$-(\text{CH}_2)_2\text{NMeC}(=\text{O})(2\text{-F-phenyl})$
S289	H	H	H	sgl	$-(\text{CH}_2)_2\text{NMeC}(=\text{O})(2,4\text{-diF-phenyl})$
S290	H	H	H	sgl	$-(\text{CH}_2)_2\text{NMeC}(=\text{O})(4\text{-F-phenyl})$
S291	H	H	H	sgl	$-(\text{CH}_2)_3(1\text{H-}1,2,3\text{-benzotriazol-}1\text{-yl})$
S292	H	H	H	sgl	$-(\text{CH}_2)_3(1\text{H-}1,2,3\text{-benzotriazol-}2\text{-yl})$
S293	H	H	H	sgl	
S294	H	H	H	sgl	
S295	H	H	H	sgl	
S296	H	H	H	sgl	$-(\text{CH}_2)_2(1\text{H-}1,2,3\text{-benzotriazol-}1\text{-yl})$
S297	H	H	H	sgl	
S298	H	H	H	sgl	$-(\text{CH}_2)_2(1\text{H-}1,2,3\text{-benzotriazol-}2\text{-yl})$
S299	H	H	H	sgl	$-(\text{CH}_2)_3(3,4\text{-dihydro-}1(2\text{H})\text{-quinolinyl})$
S300	H	H	H	sgl	$-\text{CH}_2\text{CH}_2\text{CH}=\text{CMe}(4\text{-F-phenyl})$
S301	H	H	H	sgl	$-(\text{CH}_2)_2(2,3\text{-dihydro-}1\text{H-inden-}2\text{-yl})$
S302	H	H	H	sgl	$-(\text{CH}_2)_3\text{C}(=\text{O})(2\text{-NH}_2\text{-phenyl})$
S303	H	H	H	sgl	$-(\text{CH}_2)_3\text{C}(=\text{O})(2\text{-NH}_2\text{-phenyl})$
S304	H	H	H	sgl	$-(\text{CH}_2)_3\text{C}(=\text{O})(2\text{-NH}_2\text{-}5\text{-F-phenyl})$
S305	H	H	H	sgl	$-(\text{CH}_2)_3\text{C}(=\text{O})(2\text{-NH}_2\text{-}3\text{-F-phenyl})$
S306	H	H	H	sgl	$-(\text{CH}_2)_3\text{C}(=\text{O})(2\text{-NH}_2\text{-}4\text{-Cl-phenyl})$
S307	H	H	H	sgl	$-(\text{CH}_2)_3\text{C}(=\text{O})(2\text{-NH}_2\text{-}4\text{-OH-phenyl})$
S308	H	H	H	sgl	$-(\text{CH}_2)_3\text{C}(=\text{O})(2\text{-NH}_2\text{-}4\text{-Br-phenyl})$
S309	H	H	H	sgl	$-(\text{CH}_2)_3(1\text{H-indazol-}3\text{-yl})$
S310	H	H	H	sgl	$-(\text{CH}_2)_3(5\text{-F-}1\text{H-indazol-}3\text{-yl})$
S311	H	H	H	sgl	$-(\text{CH}_2)_3(7\text{-F-}1\text{H-indazol-}3\text{-yl})$

Ex#	R7	R8	R9	b	R1
S312	H	H	H	sgl	-(CH ₂) ₃ (6-Cl-1H-indazol-3-yl)
S313	H	H	H	sgl	-(CH ₂) ₃ (6-Br-1H-indazol-3-yl)
S314	H	H	H	sgl	-(CH ₂) ₃ C(=O)(2-NHMe-phenyl)
S315	H	H	H	sgl	-(CH ₂) ₃ (1-benzothien-3-yl)
S355	H	H	H	sgl	
S356	H	H	H	sgl	-(CH ₂) ₃ (6-F-1H-indol-1-yl)
S357	H	H	H	sgl	-(CH ₂) ₃ (5-F-1H-indol-1-yl)
S358	H	H	H	sgl	-(CH ₂) ₃ (6-F-2,3-dihydro-1H-indol-1-yl)
S359	H	H	H	sgl	-(CH ₂) ₃ (5-F-2,3-dihydro-1H-indol-1-yl)
S360	H	H	H	sgl	-(CH ₂) ₃ (6-F-1H-indol-3-yl)
S361	H	H	H	sgl	-(CH ₂) ₃ (6-F-1H-indol-3-yl)
S362	H	H	H	sgl	-(CH ₂) ₃ (5-F-1H-indol-3-yl)
S363	H	H	H	sgl	-(CH ₂) ₃ (5-F-1H-indol-3-yl)
S364	H	H	H	sgl	-(CH ₂) ₃ (9H-purin-9-yl)
S365	H	H	H	sgl	-(CH ₂) ₃ (7H-purin-7-yl)
S366	H	H	H	sgl	
S367	H	H	H	sgl	-(CH ₂) ₃ (6-F-1H-indazol-3-yl)
S368	H	H	H	sgl	-(CH ₂) ₃ (6-F-1H-indazol-3-yl)
S369	H	H	H	sgl	-(CH ₂) ₃ (6-F-1H-indazol-3-yl)
S370	H	H	H	sgl	-(CH ₂) ₃ C(=O)(2-NH ₂ -4-F-phenyl)
S371	H	H	H	sgl	-(CH ₂) ₃ C(=O)(2-NH ₂ -4-F-phenyl)
S372	H	H	H	sgl	-(CH ₂) ₃ C(=O)(2-NHSO ₂ Me-4-F-phenyl)
S373	H	H	H	sgl	-(CH ₂) ₃ C(=O)(2-NHC(=O)Me-4-F-phenyl)
S374	H	H	H	sgl	-(CH ₂) ₃ C(=O)(2-NHC(=O)Me-4-F-phenyl)
S375	H	H	H	sgl	-(CH ₂) ₃ C(=O)(2-NHCO ₂ Et-4-F-phenyl)
S376	H	H	H	sgl	-(CH ₂) ₃ C(=O)(2-NHC(=O)NHEt-4-F-phenyl)
S377	H	H	H	sgl	-(CH ₂) ₃ C(=O)(2-NHCHO-4-F-phenyl)
S378	H	H	H	sgl	-(CH ₂) ₃ C(=O)(2-OH-4-F-phenyl)
S379	H	H	H	sgl	-(CH ₂) ₃ C(=O)(2-MeS-4-F-phenyl)
442	H	H	H	sgl	-(CH ₂) ₃ C(=O)(2-NHSO ₂ Me-4-F-phenyl)
485	H	H	H	sgl	-(CH ₂) ₂ C(Me)CO ₂ Me

Ex#	R7	R8	R9	b	R1
486	H	H	H	sgl	-(CH ₂) ₂ C(Me)C(OH)(4-F-phenyl) ₂
487	H	H	H	sgl	-(CH ₂) ₂ C(Me)C(OH)(4-Cl-phenyl) ₂
489	H	H	H	sgl	-(CH ₂) ₂ C(Me)C(=O)(4-F-phenyl)
490	H	H	H	sgl	-(CH ₂) ₂ C(Me)C(=O)(2-MeO-4-F-phenyl)
491	H	H	H	sgl	-(CH ₂) ₂ C(Me)C(=O)(3-Me-4-F-phenyl)
492	H	H	H	sgl	-(CH ₂) ₂ C(Me)C(=O)(2-Me-phenyl)
493	H	H	H	sgl	-(CH ₂) ₂ C(Me)C(=O)phenyl
591	Cl	H	H	sgl	-(CH ₂) ₃ C(=O)(2-NH ₂ -4-F-phenyl)

TABLE 5A



5

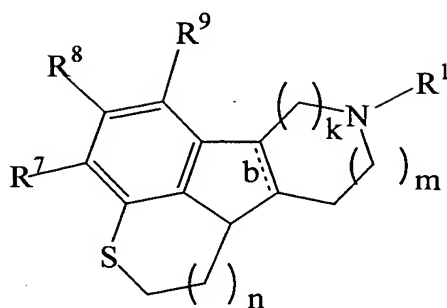
Ex#	R7	R8	R9	b	R1
115	H	H	Br	dbl	-CO ₂ -tBu
116	H	H	2,3-diCl-phenyl	dbl	-CO ₂ -tBu
117	H	H	3,4-diCl-phenyl	dbl	-CO ₂ -tBu
118	H	H	2-Cl-4-CF ₃ -phenyl	dbl	-CO ₂ -tBu
119	H	H	2,3-diCl-phenyl	dbl	H
120	H	H	3,4-diCl-phenyl	dbl	H
121	H	H	2-Cl-4-CF ₃ -phenyl	dbl	H
122	H	H	2,3-diCl-phenyl	sgl	H
123	H	H	3,4-diCl-phenyl	sgl	H
124	H	H	2-Cl-4-CF ₃ -phenyl	sgl	H
125	H	H	Br	sgl	-CO ₂ -tBu
126	H	H	2,6-diF-phenyl	sgl	-CO ₂ -tBu
127	H	H	2,6-diF-phenyl	sgl	H
128	H	2,4-diCl-phenyl	H	sgl	H
129	H	phenyl	H	sgl	H
130	H	4-F-phenyl	H	sgl	H
131	H	4-Cl-phenyl	H	sgl	H
132	H	2-Cl-phenyl	H	sgl	H
133	H	2-MeO-phenyl	H	sgl	H
134	H	2-Cl-4-CF ₃ -phenyl	H	sgl	H
135	H	2,4-diMe-phenyl	H	sgl	H
136	H	2-Cl-4-MeO-phenyl	H	sgl	H
137	H	4-iPr-phenyl	H	sgl	H

Ex#	R7	R8	R9	b	R1
138	H	4-Bu-phenyl	H	sgl	H
139	H	2-Me-4-MeO-5-F-phenyl	H	sgl	H
140	H	2-Me-4-MeO-phenyl	H	sgl	H
141	H	2-Cl-4-CF ₃ O-phenyl	H	sgl	H
142	H	2,4,5-triMe-phenyl	H	sgl	H
143	H	3-Cl-phenyl	H	sgl	H
144	H	4-Me-phenyl	H	sgl	H
145	H	2-Me-4-Cl-phenyl	H	sgl	H
146	H	2,5-diCl-phenyl	H	sgl	H
147	H	2-MeO-4-iPr-phenyl	H	sgl	H
148	H	2,6-diCl-phenyl	H	sgl	H
149	H	2,6-diF-phenyl	H	sgl	H
150	H	2-CF ₃ -4-MeO-phenyl	H	sgl	H
151	H	2-CF ₃ -phenyl	H	sgl	H
152	H	4-pyridyl	H	sgl	H
153	H	2-furanyl	H	sgl	H
154	H	2-thiophenyl	H	sgl	H
155	H	4-F-phenyl	H	sgl	H
156	H	2,3-diCl-phenyl	H	sgl	H
157	H	4-Et-phenyl	H	sgl	H
158	H	2,4-diMeO-phenyl	H	sgl	H
159	H	2-F-3-Cl-phenyl	H	sgl	H
160	H	4-MeO-phenyl	H	sgl	H
161	H	4-MeS-phenyl	H	sgl	H
162	H	4-CN-phenyl	H	sgl	H
163	H	3-CF ₃ -phenyl	H	sgl	H
164	H	2-MeO-phenyl	H	sgl	H
165	H	2-naphthyl	H	sgl	H
166	H	4-acetylphenyl	H	sgl	H
167	H	3-acetamidophenyl	H	sgl	H
168	H	2,4-diCl-phenyl	H	sgl	Me
S316	H	2,3-diMe-phenyl	H	sgl	H
S317	H	2-Me-5-F-phenyl	H	sgl	H
S318	H	2-F-5-Me-phenyl	H	sgl	H
S319	H	2-MeO-5-F-phenyl	H	sgl	H
S320	H	2-Me-3-Cl-phenyl	H	sgl	H
S321	H	3-NO ₂ -phenyl	H	sgl	H
S322	H	2-NO ₂ -phenyl	H	sgl	H
S323	H	2-Cl-3-Me-phenyl	H	sgl	H
S324	H	2-MeO-phenyl	H	sgl	H
S325	H	2,3-diCl-phenyl	H	sgl	H
S326	H	2-Cl-4-CF ₃ -phenyl	H	sgl	H
S327	H	2-Me-4-EtO-phenyl	H	sgl	H
S328	H	2-Me-4-F-phenyl	H	sgl	H
S329	H	4-Bu-phenyl	H	sgl	H
S330	H	2-CF ₃ -phenyl	H	sgl	H
S331	H	2-Cl-6-F-phenyl	H	sgl	H
S332	H	2-Cl-4-(CHF ₂)O-phenyl	H	sgl	H
S333	H	4-CF ₃ -phenyl	H	sgl	H
S334	H	4-Me-phenyl	H	sgl	H
S335	H	4-CF ₃ O-phenyl	H	sgl	H

Ex#	R7	R8	R9	b	R1
S336	H	2,4-diMeO-6-F-phenyl	H	sgl	H
S337	H	2-Me-phenyl	H	sgl	H
S338	H	2-CF ₃ -6-F-phenyl	H	sgl	H
S339	H	2-MeS-phenyl	H	sgl	H
S340	H	2,4,6-triF-phenyl	H	sgl	H
S341	H	2,4,6-triCl-phenyl	H	sgl	H
S342	H	2,6-diCl-4-MeO-phenyl	H	sgl	H
S343	H	2,3,4-triF-phenyl	H	sgl	H
S344	H	2,6-diF-4-Cl-phenyl	H	sgl	H
S345	H	2,3,4,6-tetraF-phenyl	H	sgl	H
S346	H	2,3,4,5,6-pentaF-phenyl	H	sgl	H
S347	H	2,6-diCF ₃ -phenyl	H	sgl	H
S348	H	2-CF ₃ O-phenyl	H	sgl	H
S349	H	2-CF ₃ -4-EtO-phenyl	H	sgl	H
S350	H	2-CF ₃ -4-iPrO-phenyl	H	sgl	H
S351	H	2-naphtyl	H	sgl	H
S352	H	2-CF ₃ -4-Cl-phenyl	H	sgl	H
S353	H	2-CF ₃ -4-F-phenyl	H	sgl	H
S354	H	2,4-diF-phenyl	H	sgl	Me
S380	H	2-Cl-4-EtO-phenyl	H	sgl	H
S381	H	2-Cl-4-iPrO-phenyl	H	sgl	H
S382	H	2-Et-4-MeO-phenyl	H	sgl	H
S383	H	2-CHO-4-MeO-phenyl	H	sgl	H
S384	H	2-CH(OH)Me-4-MeO-phenyl	H	sgl	H
S385	H	2-CH(OMe)Me-4-MeO-phenyl	H	sgl	H
S386	H	2-C(=O)Me-4-MeO-phenyl	H	sgl	H
S387	H	2-CH ₂ (OH)-4-MeO-phenyl	H	sgl	H
S388	H	2-CH ₂ (OMe)-4-MeO-phenyl	H	sgl	H
S389	H	2-CH(OH)Et-4-MeO-phenyl	H	sgl	H
S390	H	2-C(=O)Et-4-MeO-phenyl	H	sgl	H
S391	H	(Z)-2-CH=CHCO ₂ Me-4-MeO-phenyl	H	sgl	H
S392	H	2-CH ₂ CH ₂ CO ₂ Me-4-MeO-phenyl	H	sgl	H
S393	H	(Z)-2-CH=CHCH ₂ (OH)-4-MeO-phenyl	H	sgl	H
S394	H	(E)-2-CH=CHCO ₂ Me-4-MeO-phenyl	H	sgl	H
S395	H	(E)-2-CH=CHCH ₂ (OH)-4-MeO-phenyl	H	sgl	H
S396	H	2-CH ₂ CH ₂ OMe-4-MeO-phenyl	H	sgl	H
S397	H	2-F-4-MeO-phenyl	H	sgl	H
S403	H	2-Cl-4-F-phenyl	H	sgl	H
S405	H	(2-Cl-phenyl)-CH=CH-	H	sgl	H
S406	H	(3-Cl-phenyl)-CH=CH-	H	sgl	H
S407	H	(2,6-diF-phenyl)-CH=CH-	H	sgl	H
S410	H	cyclohexyl	H	sgl	H
S411	H	cyclopentyl	H	sgl	H
S412	H	cyclohexylmethyl	H	sgl	H
S413	H	-CH ₂ CH ₂ CO ₂ Et	H	sgl	H

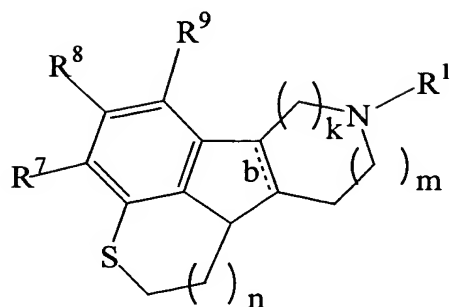
Ex#	R7	R8	R9	b	R1
S414	H	-(CH ₂) ₃ CO ₂ Et	H	sgl	H
S415	H	-(CH ₂) ₄ CO ₂ Et	H	sgl	H
S416	H	-CH ₂ CH=CH ₂	H	sgl	H
S417	H	Pr	H	sgl	H
S418	H	benzyl	H	sgl	H
S419	H	2-F-benzyl	H	sgl	H
S420	H	3-F-benzyl	H	sgl	H
S421	H	4-F-benzyl	H	sgl	H
S422	H	3-MeO-benzyl	H	sgl	H
S423	H	3-OH-benzyl	H	sgl	H
S424	H	2-MeO-benzyl	H	sgl	H
S425	H	2-OH-benzyl	H	sgl	H
S426	H	2-CO ₂ Me-3-MeO-phenyl	H	sgl	H
S427	H	2,6-diF-phenyl	H	sgl	H
S428	H	phenyl-CH=CH-	H	sgl	H
S429	H	(2-Me-4-MeO-phenyl)-CH=CH-	H	sgl	H
S430	H	-NMe ₂	H	sgl	H
S431	H	1-pyrrolidinyl	H	sgl	H
S432	H	-NTs ₂	H	sgl	H
S433	H	MeO	H	sgl	H
445	H	2-Me-4-MeO-phenyl	Me	sgl	H
446	H	2-CF ₃ -4-MeO-phenyl	Me	sgl	H
458	Me	2-CF ₃ -4-MeO-phenyl	H	sgl	H
459	Me	2,4-diCl-phenyl	H	sgl	H
460	H	3-CN-phenyl	H	sgl	H
461	H	2-Me-4-CN-phenyl	H	sgl	H
462	H	2-Me-3-CN-phenyl	H	sgl	H
463	H	2-CN-phenyl	H	sgl	H
464	H	2-CF ₃ -4-CN-phenyl	Me	sgl	H
465	H	3-CHO-phenyl	Me	sgl	H
466	H	3-CH ₂ (OH)-phenyl	Me	sgl	H
467	H	3-CH ₂ (OMe)-phenyl	Me	sgl	H
468	H	3-CH ₂ (NMe ₂)-phenyl	Me	sgl	H
469	H	3-CN-4-F-phenyl	Me	sgl	H
470	H	3-CONH ₂ -4-F-phenyl	Me	sgl	H
580	NH ₂	H	H	sgl	H
581	H	phenyl-NH-	H	sgl	H
582	phenyl-NH-	H	H	sgl	H
583	H	(4-F-phenyl)-NH-	H	sgl	H
584	H	(2,4-diCl-phenyl)-NH-	H	sgl	H
585	H	phenyl-C(=O)NH-	H	sgl	H
586	H	benzyl-NH-	H	sgl	H
587	H	phenyl-S-	H	sgl	H
588	MeO	H	H	sgl	H
589	H	2-CH ₂ (NH ₂)-4-MeO-phenyl-	H	sgl	H
590	H	2-Me-4-MeO-phenyl-	H	sgl	H
592	H	(2-Me-4-MeO-phenyl)-NH-	H	sgl	H
593	H	(2-F-4-MeO-phenyl)-NH-	H	sgl	H
595	H	(2-Me-4-F-phenyl)-NH-	H	sgl	H

TABLE 6



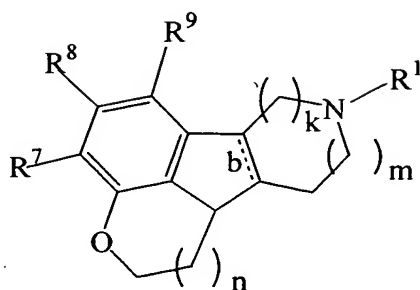
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Ex#	n	k	m	R7	R8	R9	b	R1
471	2	2	1	H	H	H	sgl	H
472	2	2	1	H	H	H	sgl	-(CH ₂) ₃ C(=O)(4-F-phenyl)
473	2	2	1	H	H	H	sgl	-(CH ₂) ₃ O(4-F-phenyl)
474	2	2	1	H	H	H	sgl	-(CH ₂) ₃ (6-F-benzisoxazol-3-yl)
475	2	2	1	H	H	H	sgl	-(CH ₂) ₃ C(=O)(4-pyridyl)
476	2	3	0	H	H	H	sgl	H
477	2	3	0	H	H	H	sgl	-(CH ₂) ₃ C(=O)(4-F-phenyl)
478	2	3	0	H	H	H	sgl	-(CH ₂) ₂ (6-F-benzisoxazol-3-yl)
483	2	2	1	H	Br	H	sgl	-(CH ₂) ₃ C(=O)(4-F-phenyl)
484	2	2	1	H	Br	H	sgl	-(CH ₂) ₃ O(4-F-phenyl)
488	1	2	1	H	Br	H	sgl	-CO ₂ -tBu

TABLE 6A

Ex#	n	k	m	R7	R8	R9	b	R1
479	2	2	1	H	2,4-diCl-phenyl	H	sgl	H
480	2	2	1	H	2-Cl-4-MeO-phenyl	H	sgl	H
481	2	2	1	H	2-Me-4-MeO-phenyl	H	sgl	H
482	2	2	1	H	Br	H	sgl	H
497	1	1	1	H	2-Cl-phenyl	H	sgl	H
498	1	1	1	H	3-Cl-phenyl	H	sgl	H
499	1	1	1	H	3-F-phenyl	H	sgl	H
500	1	1	1	H	4-Cl-phenyl	H	sgl	H
501	1	1	1	H	4-F-phenyl	H	sgl	H
502	1	1	1	H	2,3-diCl-phenyl	H	sgl	H
503	1	1	1	H	2,3-diF-phenyl	H	sgl	H
504	1	1	1	H	3,5-diCl-phenyl	H	sgl	H
505	1	1	1	H	3,5-diF-phenyl	H	sgl	H
506	1	1	1	H	3,4-diCl-phenyl	H	sgl	H
507	1	1	1	H	3,4-diF-phenyl	H	sgl	H
508	1	1	1	H	3-Cl-4-F-phenyl	H	sgl	H
509	1	1	1	H	2-F-4-Cl-phenyl	H	sgl	H

TABLE 7

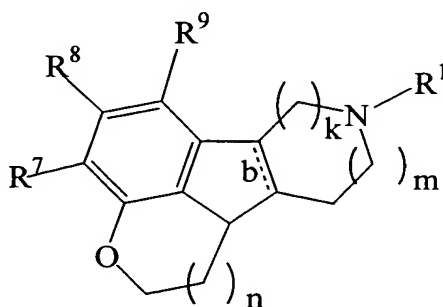


Ex#	n	k	m	R7	R8	R9	b	R1
172	2	1	1	H	H	H	sgl	H
173	1	1	1	H	2,4-diCl-phenyl	H	sgl	H
174	1	1	1	H	2-Cl-4-MeO-phenyl	H	sgl	H
436	1	1	1	H	2-Cl-phenyl	H	sgl	H
497	1	1	1	H	2-Cl-phenyl	H	sgl	H
498	1	1	1	H	3-Cl-phenyl	H	sgl	H
499	1	1	1	H	3-F-phenyl	H	sgl	H
500	1	1	1	H	4-Cl-phenyl	H	sgl	H
501	1	1	1	H	4-F-phenyl	H	sgl	H
502	1	1	1	H	2,3-diCl-phenyl	H	sgl	H
503	1	1	1	H	2,3-diF-phenyl	H	sgl	H
504	1	1	1	H	3,5-diCl-phenyl	H	sgl	H
505	1	1	1	H	3,5-diF-phenyl	H	sgl	H
506	1	1	1	H	3,4-diCl-phenyl	H	sgl	H
507	1	1	1	H	3,4-diF-phenyl	H	sgl	H
508	1	1	1	H	3-Cl-4-F-phenyl	H	sgl	H
509	1	1	1	H	2-F-4-Cl-phenyl	H	sgl	H
510	1	1	1	H	2-Cl-4-F-phenyl	H	sgl	H
511	1	1	1	H	2,5-diCl-phenyl	H	sgl	H
512	1	1	1	H	2,6-diCl-phenyl	H	sgl	H
513	1	1	1	H	2-CF ₃ -phenyl	H	sgl	H
514	1	1	1	H	4-CF ₃ -phenyl	H	sgl	H
515	1	1	1	H	2,4-diCF ₃ -phenyl	H	sgl	H
516	1	1	1	H	2-Cl-4-CF ₃ -phenyl	H	sgl	H
517	1	1	1	H	2-MeO-phenyl	H	sgl	H
518	1	1	1	H	2,4-diMeO-phenyl	H	sgl	H
519	1	1	1	H	2-MeO-5-iPr-phenyl	H	sgl	H
520	1	1	1	H	3-NO ₂ -phenyl	H	sgl	H
521	1	1	1	H	2-CHO-phenyl	H	sgl	H
522	1	1	1	H	2-CH(Me)(OH)-phenyl	H	sgl	H
523	1	1	1	H	2-CH ₂ (OH)-phenyl	H	sgl	H

Ex#	n	k	m	R7	R8	R9	b	R1
524	1	1	1	H	2-CHO-4-MeO-phenyl	H	sgl	H
525	1	1	1	H	2-OH-phenyl	H	sgl	H
526	1	1	1	H	2-CF ₃ -4-EtO-phenyl	H	sgl	H
527	1	1	1	H	2-CF ₃ -4-iPrO-phenyl	H	sgl	H
532	1	1	1	H	2-Me-4-MeO-phenyl	H	sgl	H
533	1	1	1	H	2-CF ₃ -4-MeO-phenyl	H	sgl	H
534	1	2	1	H	3,4,5-triMeO-phenyl	H	sgl	H
535	1	2	1	H	1-naphthyl	H	sgl	H
536	1	2	1	H	3-MeO-phenyl	H	sgl	H
537	1	2	1	H	2,4-diCl-phenyl	H	sgl	H
538	1	1	2	H	H	H	sgl	H
541	2	1	1	H	H	H	db1	H
542	2	1	1	H	H	H	sgl	H
543	2	1	1	H	2,6-diF-phenyl	H	sgl	H
545	1	2	1	H	H	H	sgl	H
547	2	1	1	H	2-CF ₃ -4-MeO-phenyl	H	sgl	H
548	2	1	1	H	2-Me-4-MeO-phenyl	H	sgl	H
549	2	1	1	H	2-Cl-4-CF ₃ -phenyl	H	sgl	H
550	2	1	1	H	2,3-diCl-phenyl	H	sgl	H
551	2	1	1	H	2,4-diMeO-phenyl	H	sgl	H
552	2	1	1	H	3,4-diMeO-phenyl	H	sgl	H
553	2	1	1	H	2,4-diCl-phenyl	H	sgl	H
554	2	1	1	H	3,4-diCl-phenyl	H	sgl	H
555	2	1	1	H	2,5-diCl-phenyl	H	sgl	H
556	2	1	1	H	2-CF ₃ -phenyl	H	sgl	H
557	2	1	1	H	2-Me-phenyl	H	sgl	H
558	2	1	1	H	2-Cl-phenyl	H	sgl	H
559	2	1	1	H	3-F-phenyl	H	sgl	H
560	2	1	1	H	phenyl	H	sgl	H
561	2	1	1	H	2-CF ₃ -4-EtO-phenyl	H	sgl	H
562	2	1	1	H	2-CF ₃ -4-iPrO-phenyl	H	sgl	H
563	2	1	1	H	2-MeO-4-iPr-phenyl	H	sgl	H
564	2	1	1	H	2-F-4-Cl-phenyl	H	sgl	H
565	2	1	1	H	2-Cl-4-MeO-phenyl	H	sgl	H
566	2	1	1	H	2-CHO-phenyl	H	sgl	H
567	2	1	1	H	2-CHO-4-MeO-phenyl	H	sgl	H
568	2	1	1	H	2-CH ₂ (OH)-4-MeO-phenyl	H	sgl	H
569	2	1	1	H	2-CH ₂ (OH)-phenyl	H	sgl	H
570	2	1	1	H	2-CF ₃ -4-NHMe-phenyl	H	sgl	H
571	2	1	1	H	2-CF ₃ -4-NH ₂ -phenyl	H	sgl	H
572	2	1	1	H	2-C(=O)Me-phenyl	H	sgl	H
573	2	1	1	H	2-C(=O)Me-4-MeO-phenyl	H	sgl	H

Ex#	n	k	m	R7	R8	R9	b	R1
574	2	1	1	H	2-CH(Me)(OH)-phenyl	H	sgl	H
575	2	1	1	H	2-CH(Me)(OH)-4-MeO-phenyl	H	sgl	H
576	2	1	1	H	2-CF ₃ -4-OH-phenyl	H	sgl	H
577	2	1	1	H	2-CF ₃ -4-O(C=O)Me-phenyl	H	sgl	H

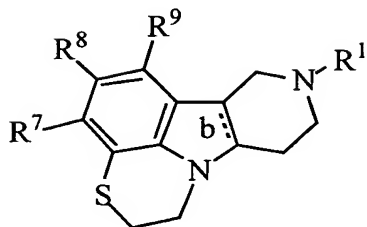
TABLE 7A



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Ex#	n	k	m	R7	R8	R9	b	R1
182	1	1	1	H	H	H	sgl	-(CH ₂) ₃ C(=O)(4-F-phenyl)
266	1	1	1	H	H	Me	sgl	-(CH ₂) ₃ C(=O)(4-F-phenyl)
270	1	1	1	H	H	H	sgl	-(CH ₂) ₃ O(4-F-phenyl)
272	1	1	1	H	H	H	sgl	H
494	1	1	1	H	H	H	sgl	-(CH ₂) ₃ C(=O)(2-NH ₂ -phenyl)
495	1	1	1	H	H	H	sgl	-(CH ₂) ₃ C(=O)(2-NH ₂ -phenyl)
496	1	1	1	H	H	H	sgl	-(CH ₂) ₃ (1H-indazol-3-yl)
528	1	1	1	H	H	H	sgl	-(CH ₂) ₃ (6-F-1H-indazol-3-yl)
529	1	1	1	H	H	H	sgl	-(CH ₂) ₃ C(=O)(2-NH ₂ -4-F-phenyl)
530	1	1	1	H	H	H	sgl	-(CH ₂) ₃ C(=O)(2-NH ₂ -4-F-phenyl)
531	1	1	1	H	H	H	sgl	-(CH ₂) ₃ C(=O)(2-OH-4-F-phenyl)
539	1	2	1	H	H	H	sgl	-(CH ₂) ₃ O(4-F-phenyl)
540	1	2	1	H	H	H	sgl	-(CH ₂) ₃ (6-F-1,2-benzisoxazol-3-yl)
544	2	1	1	H	H	H	sgl	-(CH ₂) ₃ C(=O)(4-F-phenyl)
546	1	2	1	H	H	H	sgl	-(CH ₂) ₃ C(=O)(4-F-phenyl)

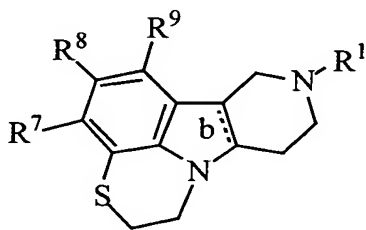
TABLE 8



Ex#	R7	R8	R9	b	R1
183	H	H	CF ₃	dbl	-(CH ₂) ₃ CH(OH)(4-F-phenyl)
184	H	H	CF ₃	dbl	-(CH ₂) ₃ C(OCH ₂ CH ₂ O)(4-F-phenyl)
185	H	H	CF ₃	sgl	-(CH ₂) ₄ (4-F-phenyl)
188	H	H	H	sgl	-(CH ₂) ₃ C(=O)(4-F-phenyl)
195	H	H	CF ₃	dbl	-(CH ₂) ₃ C(=O)(4-F-phenyl)
213	H	CH ₃	H	sgl	-(CH ₂) ₃ C(=O)(4-F-phenyl)
438	H	H	H	sgl	-(CH ₂) ₃ C(=O)(2-NH ₂ -phenyl)
439	H	H	H	sgl	-(CH ₂) ₃ C(=O)(2-NH ₂ -phenyl)
440	H	H	H	sgl	-(CH ₂) ₃ C(=O)(2-NH ₂ -4-F-phenyl)
441	H	H	H	sgl	-(CH ₂) ₃ C(=O)(2-NH ₂ -4-F-phenyl)
456	H	H	H	sgl	-(CH ₂) ₃ C(=O)(4-F-phenyl)
457	H	H	H	sgl	-(CH ₂) ₃ C(=O)(4-F-phenyl)

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TABLE 8A

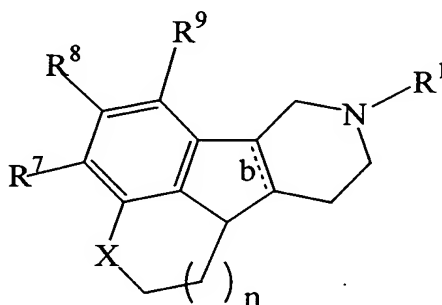


10

Ex#	R7	R8	R9	b	R1
443	2,3-diCl-phenyl	H	H	sgl	H
444	2,3-diF-phenyl	H	H	sgl	H
447	2,6-diCl-phenyl	H	H	sgl	H

Ex#	R7	R8	R9	b	R1
452	2-Me-4-MeO-phenyl	H	H	sgl	H
453	2-Cl-6-F-phenyl	H	H	sgl	H
454	2,6-diF-phenyl	H	H	sgl	H
455	2,4-diCl-phenyl	H	H	sgl	H

TABLE 9



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Ex#	X	n	R7	R8	R9	b	R1
S398	SO ₂	2	H	2,4-diCl-phenyl	H	sgl	H
S399	SO ₂	2	H	2,6-diF-phenyl	H	sgl	H
S400	SO ₂	2	H	2-Cl-phenyl	H	sgl	H
S401	SO ₂	2	H	2-F-4-MeO-phenyl	H	sgl	H
S402	SO ₂	2	H	2-Me-4-MeO-phenyl	H	sgl	H
S404	SO	2	H	2-Cl-4-F-phenyl	H	sgl	H
S434	SO	2	H	2,4-diCl-phenyl	H	sgl	H
S435	SO	2	H	2-Me-4-MeO-phenyl	H	sgl	H
448	SO ₂	1	H	H	H	sgl	H
449	SO	1	H	H	H	sgl	H
450	SO ₂	1	H	2-CF ₃ -4-MeO-phenyl	H	sgl	H
451	SO ₂	1	H	2,4-diCl-phenyl	H	sgl	H